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JOURNAL OF GERONTOLOGY

VOLUME 5 OCTOBER, 1950 NUMBER 4

Studies of Adrenal Cortical and Anterior Pituitary Function in Elderly Men

DAVID H. SOLOMON AND NATHAN W. SHOCK

THE RESULTS OF THIS STUDY INDICATE A DECREASED ACTH OUTPUT OF THE ANTERIOR PITUITARY IN THE AGED IN RESPONSE TO EPINEPHRINE ADMINISTRATION. THE ABILITY OF THE ADRENAL CORTEX TO SECRETE HORMONES OF THE 11-17-OXYSTEROID GROUP UNDER ACTH STIMULATION IS, HOWEVER, NOT GROSSLY IMPAIRED IN SENESCENCE. THE RENAL HANDLING OF URIC ACID IN RESPONSE TO ADRENAL CORTICAL "S" IS ALTERED IN THE AGED. THIS PAPER WAS PRESENTED IN PART AT THE SECOND ANNUAL MEETING OF THE GERONTOLOGICAL SOCIETY, INC. IN CHICAGO, NOVEMBER 5-6, 1949.

ALTHOUGH endocrine changes have long been postulated as a cause or accompaniment of aging (3, 8, 34), gonadal failure has remained the only endocrine alteration demonstrated to be characteristic of old age. The present study is a preliminary investigation of the state of function of the anterior pituitary and the adrenal cortex in the aged.

Anatomically, the weight of the anterior pituitary and of the adrenal cortex declines after the age of 50 in men and women (27, 29). In the anterior pituitary of the aged, the acidophil cells are reduced in number and show less histologic evidence of secretory activity, while chromophobe cells increase correspondingly in number (23, 27, 37). The percentage of basophil cells increases slightly in women in the seventh and eighth decades but remains unchanged in men (27). Vacuolation of basophils becomes more prominent, and invasion of the posterior lobe by basophils is a frequent finding in the aged (7, 21, 32). The fibrillar tissue lining pituitary sinusoids increases in thickness (20). The adrenal cortex shows fibrosis and a decrease in the number of epithelial cells in aged men (5), while an increase in the thickness of reticulum and in the incidence of nodular hyperplasia have been noted in rats (6, 38).

Gross clinical abnormalities of the anterior pituitary and the adrenal cortex do not increase in incidence in senescence (3, 35). However, the presence of some degree of either hyperfunction (8, 22) or hypofunction (3, 13) of each organ has been suggested by clinical observations on the aged. Findlay (8) has recently emphasized the similarity of certain aspects of senescence to Cushing's syndrome and has suggested the existence in the aged of pituitary hyperacidophilism and adrenal cortical hyperfunction with respect to "S" hormone. He proposed an increased tissue sensitivity to cortical hormones in the aged as an alternative possibility.

Pertinent physiologic studies are few. Regarding the anterior pituitary, Perlmutter and Riggs (24) obtained evidence that the decline in basal metabolic rate with age may depend on a decreased pituitary output of TSH secondary to decreased tissue demands. Excretion of FSH in the urine of the aged woman and the castrate man is increased (1, 11), but the actual pituitary output of FSH and LH may not be increased (14). With regard to the

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adrenal cortex, Pincus and associates (26) have noted no significant change with age in the nocturnal excretion of neutral reducing steroids. Some increase in variability in diurnal steroid excretion was observed in the aged. The well-confirmed decline in urinary 17-ketosteroid excretion in the aged men (12, 18, 19, 26) cannot be interpreted as decreased adrenal androgen output in view of the testicular origin of a portion of these metabolites. No systematic study of 17-ketosteroid excretion in elderly women is as yet available.

In the present study, the responsiveness of the anterior pituitary and of the adrenal cortex in young and aged men was evaluated by measuring the response to stimuli which demand secretory activity. The response to epinephrine was used as a test of pituitary capacity to secrete adrenocorticotrophic hormone (ACTH), while the response to exogenous ACTH was used to test adrenal cortical capacity to secrete steroid hormones under stimulation.

Methods

Subjects.—Thirty young men (aged 20 through 44) and 26 elderly men (aged 61 through 89) were studied. The subjects included laboratory personnel, convalescent patients in the Baltimore City Hospitals, and residents of the Infirmary Division (Home for the Aged). Twenty-seven young and all 26 aged subjects were given ACTH, and 2 subjects from each age group were also given cortisone. Thirteen aged subjects who received ACTH were also tested with epinephrine, while 12 young subjects who received ACTH and 3 who did not were given epinephrine. Of the subjects receiving epinephrine, 4 young and 6 aged were given saline as a control on a different day.

Subjects were excluded who gave evidence by history or physical examination of renal, adrenal, thyroid, or pituitary disease; congestive heart failure; diastolic hypertension; blood dyscrasias; gout or diabetes; or who showed any of the following laboratory findings: (a) blood hemoglobin less than 12 gm. per cent; (b) evidence of blood dyscrasia in stained smear; (c) urinalysis (morning specimens) showing the presence of erythrocytes, casts, or qualitatively-detectable sugar or protein; (d) fasting blood sugar greater than 105 mg. per cent; (e) blood non-protein nitrogen greater than 40 mg. per cent; or (f) basal blood eosinophil count under 50 or over 400 cells per cubic millimeter. Many aged subjects were included who had evidence of benign prostatic hypertrophy, generalized arteriosclerosis, arteriosclerotic heart disease, or testicular atrophy.

Test Procedure.—The procedures of Thorn and associates (36) and Recant and associates (28) were employed. Subjects remained in bed throughout the test. Twenty-five mg. of ACTH (Armour Lot G-1012, equivalent of

18 mg. of Standard LA-1-A ACTH) or 100 mg. of cortisone acetate were administered intragluteally at 8 a.m. Four-tenths mg. of epinephrine in 200 cc. of saline or saline alone were infused intravenously from 8 to 9 a.m. Venous blood samples for uric acid, potassium, and hematologic determinations were obtained at 8 a.m. and at 12 noon. Additional blood samples (venous) for hematologic study were obtained at 9, 10, and 11 a.m. in all epinephrine and saline tests and in 25 of the ACTH tests. Voided urine specimens were obtained from 6 to 8 a.m. and from 9 a.m. to 12 noon. A small breakfast (100 cc. of orange juice, 2 slices of toast, and 200 cc. of coffee) was consumed at 8:15 a.m. in the ACTH and cortisone tests and at 9:15 a.m. in the epinephrine and saline tests.

Laboratory Methods.—NBS certified pipettes and hemocytometers were used for all blood counts. Eosinophil counts were made by the method of Dunger as modified by Forsham and associates (9). The correlation coefficient between paired counts on 130 blood samples, where each count consisted of 4 fields, was 0.99; while that between 2 halves of the same count was only 0.96. This difference reduced the standard error of estimate for 130 counts (mean count = 154) from 32 to 16 cells per cubic millimeter. Hence the accepted procedure of using 4 fields for a single count cannot be shortened except for problems requiring very low accuracy.

White blood counts were made in duplicate. Total neutrophils and lymphocytes were estimated from the WBC multiplied by percentages obtained from 200-cell differential counts on Wright's stained films. Urine creatinine was determined by the method of Peters (25) and plasma and urine acid by the method of Archibald as described by Forsham and associates (9). Potassium in plasma and urine was analyzed with the Beckman Flame Photometer. Urine samples were prepared for analysis by dilution, while 1 cc. samples of plasma were ashed and diluted prior to analysis. Normal propyl alcohol was added to the solutions to assure even flow through the atomizer. Sodium determinations were made and potassium standards and solutions were brought to the same concentration (mEq./L.) of sodium prior to potassium analysis.

Analysis of Results.—Forsham and associates (9) noted that the degree of absolute eosinophil fall produced by ACTH was related to the pre-existing basal value. They believed it necessary to minimize this relation, if possible, in expressing their post-ACTH changes, since the basal values themselves did not seem to reflect levels of adrenal cortical function except in markedly abnormal cases, e.g., Cushing's syndrome. In order to extend this approach to several of the indices of adrenal cortical function used in the present study, correlation coefficients were determined for the relationship between basal value and absolute and percentage post-ACTH change (table 1). The measure of response which gave the lower correlation with the basal value was chosen for the expression of our results, viz., per cent fall in eosinophils and lymphocytes, per cent rise in neutrophils, and absolute increase in urinary uric acid/creatinine and potassium/creatinine ratios.

TABLE 1. CORRELATION COEFFICIENTS BETWEEN BASAL VALUES AND POST-ACTH CHANGES IN VARIOUS INDICES OF ADRENAL CORTICAL FUNCTION

Measurement	Number of Cases	Basal Value vs. Absolute Increase or Decrease	Basal Value vs. Per Cent Increase or Decrease
Eosinophils	48[1]	+0.87 (S)[2]	+0.05
Lymphocytes	48	+0.66 (S)	+0.39 (S)
Neutrophiles	50	+0.36 (S)	+0.05
Uric Acid/Creatinine	48	−0.09	−0.51 (S)
Potassium/Creatinine	29	+0.03	−0.47 (S)

[1] The correlations are presented for cases from both age groups combined, since no significant age differences were found in the correlation coefficients.
[2] (S) = $P < 0.02$.

In the first 3, our method of expression was the same as that of Forsham and associates. In the 2 urinary excretion measures, the indicated method of expression was the abso-

lute increase, although a per cent expression has become customary. For completeness, urinary excretion responses were reported in both ways in this paper.

All comparisons of the age groups were evaluated by a t-test for unmatched samples.

Results

Basal Values.—The pre-ACTH values were alike in the 2 age groups in all hematologic indices (table 2). The basal urinary excretion rates for uric acid, potassium, and creatinine were all decreased in the aged. There was a relatively greater depression in creatinine excretion than in uric acid and potassium. This resulted in basal uric acid/creatinine and potassium/creatinine ratios which were greater in the aged than in the young (table 2). Plasma uric acid and potassium levels were alike in the young and the aged.

Responses to ACTH.—The changes which followed the administration of ACTH in the

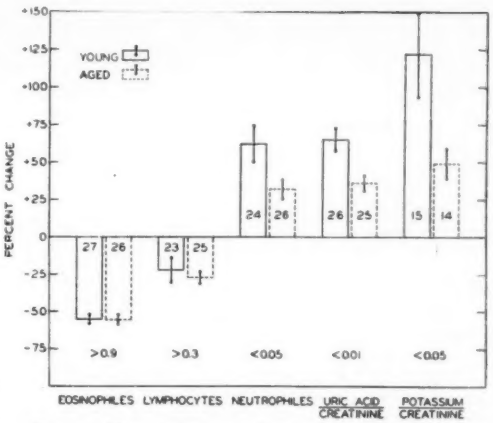

FIG. 1. The responses of young and aged men to the administration of 18 mg. of ACTH.

The ordinate represents the per cent change from basal value during the four hours after ACTH administration. The bar ending each column indicates the mean; the circles indicate the standard error of the mean. The number of cases analyzed is shown within the columns. The probability of the chance occurrence of the observed difference is shown below each pair of columns.

TABLE 2. AGE COMPARISONS IN BASAL VALUES FOR INDICES OF ADRENAL CORTICAL RESPONSE

Index	Young		Old		Significance of Age Difference
	Number of Cases	Mean ± σ_M[1]	Number of Cases	Mean ± σ_M	
Blood Eosinophils (cells/cu. mm.)	27	160 ± 12.8	26	159 ± 16.6	NS[2]
Blood Lymphocytes (cells/cu. mm.)	23	1610 ± 89.7	25	1450 ±103	NS
Blood Neutrophils (cells/cu. mm.)	24	4270 ±306	26	3900 ±215	NS
Uric Acid Excretion Rate (mg./min./1.73 sq. m.)	23	0.49± 0.036	22	0.38± 0.036	PS
Potassium Excretion Rate (mg./min./1.73 sq. m.)	13	2.2 ± 0.27	13	1.4 ± 0.20	PS
Creatinine Excretion Rate (mg./min./1.73 sq. m.)	23	1.21± 0.083	22	0.76± 0.073	S
Urine Uric Acid/Creatinine	26	0.44± 0.027	25	0.51± 0.024	PS
Urine Potassium/Creatinine	15	1.8 ± 0.23	14	2.2 ± 0.24	NS
Plasma Uric Acid (mg. %)	11	4.7 ± 0.39	9	4.8 ± 0.17	NS
Plasma Potassium (mEq./L.)	15	4.2 ± 0.05	9	4.0 ± 0.22	NS

[1] σ_M = Standard error of the mean

[2] NS = P > 0.05, PS = P < 0.05 and > 0.02, S = P < 0.02

TABLE 3. AGE COMPARISON IN INDICES OF ADRENAL CORTICAL RESPONSE AFTER ACTH (18 MG.)

Response	Young		Old		Significance of Age Difference
	Number of Cases	Mean ± $\sigma_{\overline{M}}$[1]	Number of Cases	Mean ± $\sigma_{\overline{M}}$	
Per Cent Fall in Eosinophils in 4 Hours	27	55 ± 2.9	26	55 ± 2.9	NS[2]
Per Cent Fall in Lymphocytes in 4 Hours	23	22 ± 7.8	25	27 ± 4.2	NS
Per Cent Rise in Neutrophils in 4 Hours	24	62 ± 12	26	32 ± 6.2	PS
Absolute Rise in Uric Acid Excretion Rate (mg./min./1.73 sq. m.)	23	0.22± .033	22	0.09± 0.039	S
Absolute Rise in Uric Acid/Creatinine	26	0.26± 0.020	25	0.18± 0.020	S
Per Cent Rise in Uric Acid/Creatinine	26	65 ± 7.4	25	36 ± 5.0	S
Absolute Rise in Potassium Excretion Rate (mg./min./1.73 sq. m.)	13	1.6 ± 0.38	13	0.48± 0.28	S
Absolute Rise in Potassium/Creatinine	15	1.8 ± 0.27	14	1.0 ± 0.22	PS
Per Cent Rise in Potassium/Creatinine	15	122 ± 28	14	49 ± 9.6	PS
Absolute Fall in Creatinine Excretion Rate (mg./min./1.73 sq. m.)	23	0.18± 0.076	22	0.02± 0.068	NS
Fall in Plasma Uric Acid (mg. %)	11	0.15± 0.10	19	0.14± 0.06	NS
Rise in Plasma Potassium (mEq./L.)	9	0.05± 0.07	15	0.09± 0.10	NS

[1] $\sigma_{\overline{M}}$ = Standard error of the mean

[2] NS = $P > 0.05$, PS = $P < 0.05$ and > 0.01, S = $P < 0.01$

2 age groups are compared in table 3 and figure 1. The mean per cent decline in eosinophils four hours after ACTH was 55 per cent in both groups. The frequency distributions for the 2 age groups were essentially superimposible (fig. 2). Thus, whatever arbitrary minimal figure is set for the normal response to ACTH, the same number of young and aged subjects would fall below it. In subgroups of 11 young and 14 aged subjects in whom hourly counts were made for four hours after ACTH administration, the rates of fall were not different in the 2 age groups (fig. 3).

The decline in lymphocytes averaged 22 per cent in the young and 27 per cent in the aged, an insignificant difference. The mean per cent rise in neutrophils was significantly greater in the young than in the aged, 62 per cent as against 32 per cent.

The post-ACTH rise in uric acid/creatinine ratio was significantly greater for the young group than for the old, whether expressed as an absolute or a per cent increase. An age difference also existed for the degree of rise in uric acid excretion rate, uncorrected or corrected for surface area. Creatinine excretion rate and plasma uric acid concentration fell slightly (table 3). No age differences were present.

In the young, the degree of rise in uric acid/creatinine ratio was significantly correlated with the per cent fall in eosinophils ($r = +0.47$), whereas in the aged group the correlation was lower and not significant ($r = +$

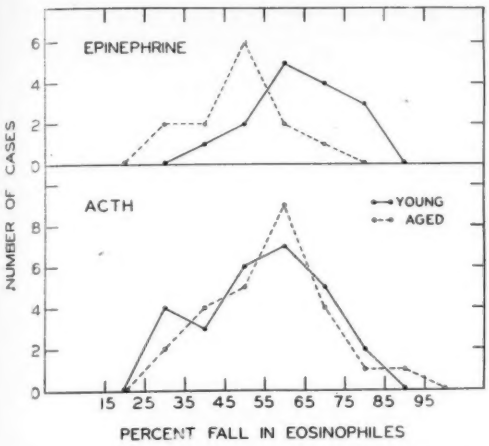

FIG. 2. The frequency polygons for the eosinopenic responses to epinephrine and ACTH in young and aged men.

The measure of response used for the epinephrine plot was the per cent decline from maximum to minimum eosinophil count, while that used for ACTH was from basal values to values obtained four hours after administration of ACTH.

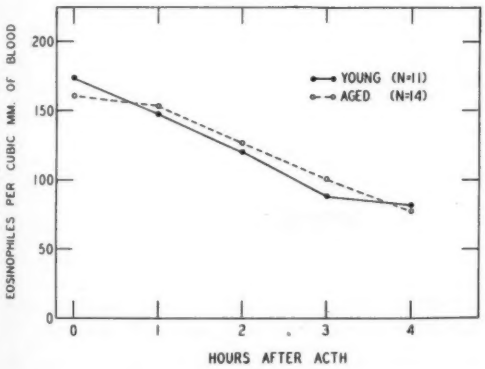

FIG. 3. Mean curves of blood eosinophils after ACTH administration in young and aged men.

Each point on the solid and dotted-line curves represents the mean of counts on 11 young men and 14 elderly men, respectively. At time zero, 18 mg. of ACTH were given intramuscularly. Absolute eosinophil counts were plotted here since the initial levels were essentially identical in young and aged subjects.

0.26). On the other hand, the rise in uric acid/creatinine ratio did not seem related to a measure of renal function (basal glomerular filtration rate) in 7 young persons, while in 9 elderly persons the degree of change in uric acid/creatinine ratio seemed clearly related to the basal GFR (fig. 4).

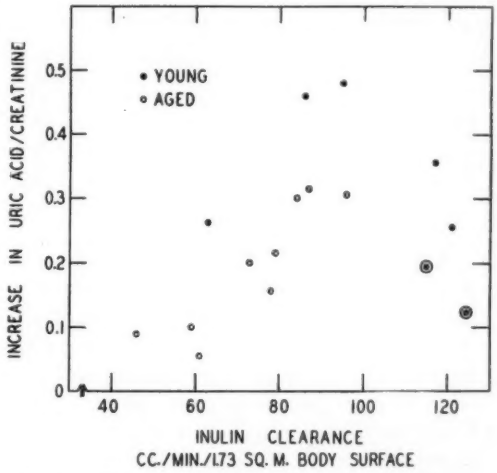

FIG. 4. The relationship between glomerular filtration rate (inulin clearance) and the degree of rise in uric acid/creatinine ratio after ACTH administration.

Note the tendency for poor uric acid/creatinine responses to occur in aged individuals with inulin clearances which are "low," though within the usual range for their age (4). The encircled points at the right are instances in which no lymphocyte fall occurred after ACTH, which may account for the failure of uric acid response in the presence of normal renal function.

The post-ACTH potassium diuresis, like that for uric acid, was significantly greater in the young group than in the aged. Plasma potassium rose insignificantly in both age groups.

Responses to Cortisone.—When 2 young subjects with previous normal responses to ACTH were given cortisone, they showed a 32 and 45 per cent eosinophil fall and a rise in uric acid/creatinine ratio of 0.22 (+ 89 per cent) and 0.19 (+ 45 per cent), respectively. Two elderly men in whom ACTH had produced a normal eosinophil fall but a deficient uric acid/creatinine rise demonstrated no rise in uric acid/creatinine ratio after cortisone, although an eosinophil fall occurred (table 4).

TABLE 4. RESPONSES OF SELECTED YOUNG AND AGED SUBJECTS TO ACTH (18 MG.) AND CORTISONE ACETATE (100 MG.)

Subject	Age	ACTH			CORTISONE		
		Eosinophil Fall Per Cent	Rise in Uric Acid/Creatinine		Eosinophil Fall Per Cent	Rise in Uric Acid/Creatinine	
			Absolute	Per Cent		Absolute	Per Cent
R. F.	23	60	0.25	45	32	0.22	89
D. S.	27	78	0.34	105	45	0.19	45
V. L.	89	74	0.10	25	71	−0.01	− 2
J. C.	84	57	0.003	1	36	−0.03	− 6

Responses to Epinephrine.—Whereas the eosinopenia produced by ACTH was in all respects identical in the young and aged, that which followed epinephrine administration was significantly less in the aged than in the young. This was true for the per cent fall from initial count to four-hour count, from initial count to the minimum of hourly counts, or from the maximum to the minimum count (table 5 and fig. 5). The frequency distributions for maximum to minimum eosinophil responses to epinephrine show the shift of the aged distribution toward low responses (fig. 2). The general time course of the reaction was alike in the two age groups (fig. 6).

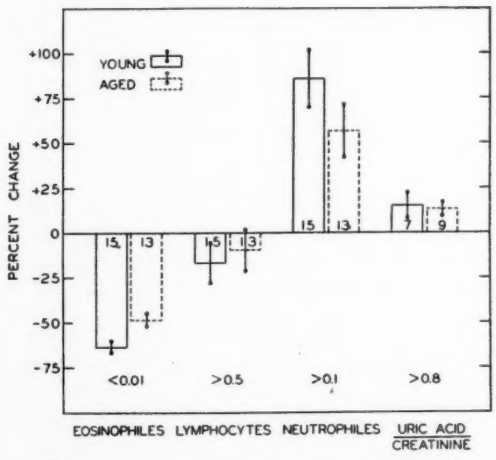

FIG. 5. The responses of young and aged men to the administration of 0.4 mg. of epinephrine intravenously.

Notation the same as for Figure 1. For eosinophils, per cent fall from maximum to minimum count has been plotted. For age differences in eosinophil responses when otherwise expressed, see table 3.

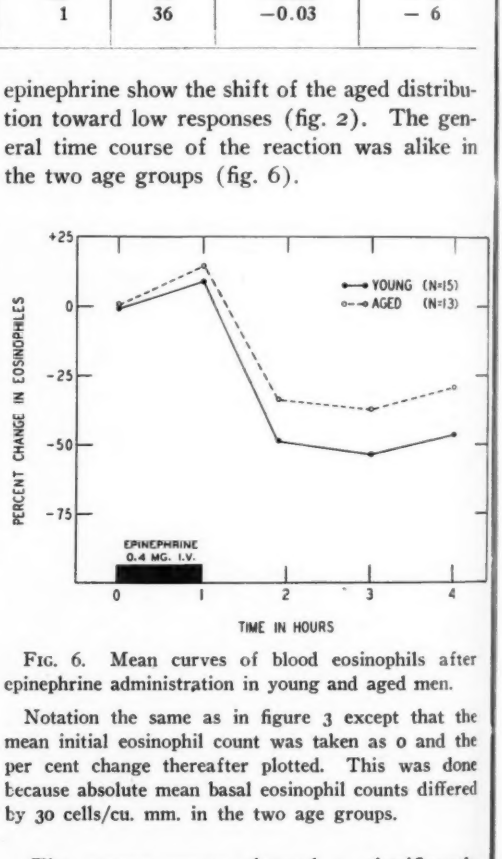

FIG. 6. Mean curves of blood eosinophils after epinephrine administration in young and aged men.

Notation the same as in figure 3 except that the mean initial eosinophil count was taken as 0 and the per cent change thereafter plotted. This was done because absolute mean basal eosinophil counts differed by 30 cells/cu. mm. in the two age groups.

The young group showed a significantly greater absolute rise in neutrophils than the aged. The other indices were not strikingly affected by epinephrine. Lymphocytes did not fall significantly in either age group. Mean uric acid/creatinine ratio was significantly greater after epinephrine than before in 16

TABLE 5. AGE COMPARISONS IN INDICES OF ADRENAL CORTICAL RESPONSE AFTER EPINEPHRINE (0.4 MG.)

Response	Young		Old		Significance of Age Difference
	Number of Cases	Mean ± $\sigma_{\overline{M}}$	Number of Cases	Mean ± $\sigma_{\overline{M}}$[1]	
Per Cent Fall in Eosinophils from Maximum Count to Minimum Count	15	64 ± 3.3	13	49 ± 3.4	S[2]
Per Cent Fall in Eosinophils from Initial Count to Minimum Count	15	59 ± 4.3	13	40 ± 3.3	S
Per Cent Fall in Eosinophils from Initial Count to 4-Hour Count	15	48 ± 5.5	13	28 ± 4.7	PS
Per Cent Fall in Lymphocytes from Initial Count to 4-Hour Count	15	17 ± 8.0	13	10 ± 11	NS
Per Cent Rise in Neutrophils from Initial Count to 4-Hour Count	15	86 ± 16	13	57 ± 14	NS
Absolute Rise in Neutrophils	15	2870 ±418	13	1700 ±311	PS
Per Cent Rise in Uric Acid/Creatinine	7	17 ± 7.3	9	13 ± 3.6	NS

[1] $\sigma_{\overline{M}}$ = Standard error of the mean

[2] NS = P > 0.05, PS = P < 0.05 and < 0.02, S = P < 0.02

subjects of both age groups, but the rise was small and not significantly different from that which occurred in 10 control subjects given saline.

Twelve young subjects and 13 old subjects from among the experimental groups received ACTH and epinephrine on consecutive days. The order of administration was randomized. Defining the individual's response as his maximum per cent eosinophil decline and subtracting this response figure for ACTH from that for epinephrine, an average difference of +9 response units was found in the young and −5 units in the aged. Expressed as a per cent of the ACTH response, the young group showed a 17 per cent greater response to epinephrine than to ACTH, while the aged group averaged 9 per cent lower for epinephrine than for ACTH. This difference between the 2 age groups in comparative responses to ACTH and epinephrine was significant (table 6).

TABLE 6. AGE COMPARISON OF THE RELATIVE DEGREE OF EOSINOPENIA IN RESPONSE TO ACTH AND EPINEPHRINE

Group	Number of Cases	Maximum Per Cent Fall		
		Epinephrine	ACTH	Difference[1] ± S.E. Difference
Young	12	64.3	55.6	8.7±4.5
Aged	13	48.5	54.1	−5.6±4.2
T Score for Age Difference				2.32
P Value for Age Difference				<0.05

[1] Each subject's ACTH response (per cent fall in eosinophils) was subtracted from his epinephrine response. The resulting differences were averaged and the standard errors calculated for each age group.

DISCUSSION

ACTH is without physiologic effect in the adrenalectomized animal (9). Among the indices studied here, all are unaffected by ACTH in the human Addisonian except for the neutrophil count, which may rise moderately (9). A quantitative relation exists be-

tween adrenal "S" hormone dose and per cent eosinopenia within submaximal dosage ranges (33). The dose of ACTH used in the present studies induced secretion by the adrenal of amounts of "S" hormone which were submaximally eosinopenic, as judged by comparison of the mean of the present series with others using larger doses (9, 15) and as supported by the normality of the present distributions of eosinopenic responses. Thus, the equal means and distributions for eosinophil responses in the young and aged groups in the present study may be interpreted as reflecting the secretion of approximately equal quantities of adrenal cortical "S" hormone in response to ACTH in the 2 groups.

In this light, the deficient uric acid diuresis in the aged must have been on a peripheral basis, a suggestion which is supported by the failure of selected aged persons to show a normal uric acid diuresis after cortisone. The uric acid diuresis in response to adrenal cortical activity is believed to depend upon an increased rate of nucleoprotein catabolism (reflected by lymphopenia) and an increased renal clearance of uric acid (9, 17). At the dosage of the present study, the latter seems to have predominated since lymphocyte fall was small on the average and did not correlate with the rise in uric acid/creatinine ratio in either age group ($r = +0.32$ for young, -0.01 for aged, $+0.20$ for total). In addition, plasma uric acid tended to fall even when urinary excretion rose but slightly, indicating that little excess supply of uric acid could have been present. Finally, a renal mechanism for the impairment of uric acid diuresis in the aged is suggested by the relation found between the rise in uric acid/creatinine ratio and a measure of renal function (GFR).

This evidence does not in any way indicate which segment of the kidney might be involved since renal functions other than glomerular filtration rate decline with age (4) and since both glomerular filtration and tubular activity are factors in creatinine and uric acid excretion (2).

Potassium diuresis after ACTH may depend on adrenal cortical secretion of both "S" hormone and salt-regulating hormone. Thus, although renal impairment may well be the principal explanation for the deficient potassium response in the aged, the possibility of decreased DCA-like hormone cannot be excluded.

Creatinine clearances were not measured in the present study. It is of interest, nevertheless, that the fall in creatinine excretion rate which was observed after ACTH is consistent with the observation by Ingbar and associates (17) that creatinine clearance usually falls although inulin clearance rises after ACTH.

Neutrophilia was less in the aged than in the young after ACTH and epinephrine. Since the neutrophilia after ACTH depends in part on adrenal factors and in part on unknown factors (9), the deficiency in the aged could be caused by a lower adrenal "S" hormone output, lower production of the "unknown factors," or diminished bone marrow responsiveness to a normal amount of the factors which stimulate neutrophil production or release. The first possibility can be excluded in the light of the eosinophil data, but the second and third are equally possible. It is of interest that a young and an old group studied in this laboratory showed no difference in their neutrophil response to the intravenous administration of 50,000,000 killed typhoid organisms. However, the sensitivity of bone marrow to the much milder stimulus represented by the post-ACTH effect could still be impaired in the aged.

The interpretation of the responses to epinephrine rests wholly on the eosinophil changes, since the acute effects of epinephrine on four-hour lymphocyte counts and on urinary uric acid/creatinine ratio were small and inconsistent in the present studies. Recant and his associates (28) made similar observations on both lymphocytes and urinary uric acid, while Gabrilove and associates (10) were unable to distinguish normals from patients with Addison's disease on the basis of the degree of post-epinephrine lymphopenia.

Eosinopenia after epinephrine was less in the aged than in the young. No data exist

to demonstrate a quantitative relation between the amount of ACTH supplied by the pituitary and the degree of eosinopenia. Since adrenal "S" hormone dose and eosinopenia are quantitatively related and since the eosinopenia after epinephrine is mediated through a pituitary output of ACTH and its effect on adrenal hormone output (28), it is likely that the deficient eosinopenia after epinephrine seen in the aged represents reduced secretion of ACTH in response to the stimulus. The site of this deficiency cannot be localized within the pituitary secretory cells (presumably the acidophils) since hypothalamic activity (16) and the degree of tissue utilization of cortical hormones (30) may also influence the discharge of ACTH by the pituitary.

Although the response of the pituitary to acute epinephrine stimulation, however mediated, seems to be quantitatively reduced in the aged, the long-term pituitary output of ACTH cannot be notably reduced, since normal functional responsiveness of the adrenal cortex is maintained.

It may be proposed that the clinical failure of senile persons to withstand stresses which are nonlethal in young persons is caused by a deficient pituitary-adrenal response to such stresses. The observed deficiency in pituitary activation by epinephrine in the aged is suggestive in this regard, but it cannot be directly applied as evidence since the mechanism of pituitary-adrenal response to nonspecific stresses may not be identical with that to epinephrine (28). Furthermore, caution is indicated by the fact that, although adrenal cortical hyperfunction is characteristic of the response of the organism to stress (31), it has by no means been established that a moderate lessening of the magnitude of this response is associated with increased mortality.

Summary

1. Adrenal cortical responsiveness was evaluated in 27 young men and 26 aged men who were given 18 mg. of ACTH, and pituitary responsiveness was tested in 15 young men and 13 aged men who received 0.4 mg. of epinephrine. Eosinophil, lymphocyte, and neutrophil counts were made, and urinary uric acid, potassium, and creatinine excretions were measured before and after hormone administration.

2. There was no age difference in the eosinopenia after ACTH, but epinephrine produced significantly greater eosinophil depression in the young than in the aged.

3. The aged showed significantly smaller responses to ACTH than the young in the following: (a) the rise in neutrophils; (b) the rise in uric acid excretion and uric acid/creatinine ratio; and (c) the rise in potassium excretion and potassium/creatinine ratio.

4. The neutrophilia after epinephrine was also less marked in the aged than in the young.

5. Two aged subjects showed no rise in urinary uric acid/creatinine ratio when eosinopenia was produced by the administration of cortisone acetate.

6. The results suggest in the aged a decreased ACTH output by the anterior pituitary in response to epinephrine stimulation. On the other hand, it is concluded that the ability of the adrenal cortex to secrete hormones of the 11-17-oxysteroid group under ACTH stimulation is not grossly impaired in senescence and thus that the long-term rate of ACTH output by the anterior pituitary is sufficient to maintain the gross functional integrity of the adrenal cortex.

7. The renal handling of uric acid in response to adrenal cortical "S" hormone seems to be altered by aging.

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Atheromatosis as a Sequel to Senescent Changes in the Arterial Wall

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DOCTORS LANSING, ALEX, AND ROSENTHAL PRESENT NEW EVIDENCE TO SUPPORT THEIR VIEW THAT ARTERIOSCLEROSIS IS NOT A SINGLE DISEASE BUT HAS AT LEAST TWO WELL DEFINED COMPONENTS. THESE ARE, FIRST, AGING OF THE ARTERIAL WALL AND SECOND, CHOLESTEROL ACCUMULATION IN INTIMAL SCARS.

We have previously defined arteriosclerosis as an age dependent process of fatty and fibrotic degeneration of the intima accompanied by and generally preceded by calcification of medial elastic tissue (5). This definition rests largely on qualitative and semi-quantitative observations which indicated that calcification of the media generally precedes the formation of intimal plaques and that intimal plaques do not occur in the absence of medial damage (1); that in the human coronary artery there is progressive increase of calcium with age in the media, this calcium being concentrated in or on the elastic fibers (6); that in the human aorta there is a similar concentration of calcium in the elastic fibers of the media (5), while the pulmonary artery, which rarely exhibits atheromata, is notable for a greatly retarded and reduced degree of calcification of medial elastic tissue (7).

In order to put our views on a firmer basis we undertook quantitative chemical analyses for calcium and cholesterol evaluating two important variables—age of the individual and severity of the lesion. Present analyses indicate quite clearly that calcification of medial elastic tissue is a function of age with or without intimal change and that, in a series of plaques graded by severity, calcification of medial elastic tissue occurs prior to the deposition of cholesterol.

Analytic Scheme No. 1—Atheroma-Free Age Series

We have regarded the alteration in structure and chemistry of elastic fibers, particularly calcification, as accompanying the aging of arteries. This senescent change may be complicated by secondary processes such as intimal hyperplasia, fatty degeneration, and massive necrotic calcification.

If the calcification of elastic fibers in the arterial wall is the primary event, both chronologically and etiologically, then we would expect to find this change in a series of aortas graded by age irrespective of the condition of their intimas. In particular, we would expect atheroma-free areas of a graded age series to manifest a progressive rise in the calcium content of their medial elastic tissues.

Materials and Methods.—Human aortas were obtained at autopsy. Atheroma-free segments of the upper abdominal portions were excised and both the adventitia and intima were stripped from the media. To guard against chemical contamination of the selected areas by adjacent and overlying necrotic and calcified plaques we selected for analysis 14 aortas which possessed an over-all minimum of atheromata.

Elastin was determined by a modification of Lowry's method which we have previously described (8). The method of Salomon, Gabrio, and Smith (10) was used for the semimicrodetermination of calcium. In our experience this procedure yields an error not exceeding 5 per cent. Total cholesterol was determined by the method of Kingsley and Schaffert (4) with no modifications.

Observations.—The data obtained in the analyses of the separated intimas and medias are summarized as follows:

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Dr. Alex is research assistant in the Department of Anatomy, Washington University School of Medicine. He received his M.D. degree in 1943 from Washington University School of Medicine. He was interne, assistant resident, and resident in Medicine, Jewish Hospital, St. Louis, 1943-1946, served in the Armed Forces 1946-1948 in the Phillipines, and was resident in pathology, 1948-1949, Jewish Hospital, St. Louis. His research is largely in the field of arteriosclerosis.

Dr. Rosenthal is research associate in the Department of Anatomy, Washington University School of Medicine. He received his Ph.D. degree in 1941 from Yale. From 1941 to 1945 he served with the Army Air Force as an aviation physiologist. He was a research associate at Barnard Free Skin and Cancer Hospital, St. Louis, 1946-1948, before taking his present position. Biophysics and cancer are his chief research interests.

The salient feature of these analyses is that the thirty-fold increase with age in calcium content of medial elastin occurs uniformly and regularly in contrast with the poor correlation obtained in the analyses for intimal and medial cholesterol and intimal calcium.

This demonstration eliminates the possibility that the medial calcium could have infiltrated from pre-existing calcified intimal plaques. We conclude that arteriosclerosis is a disease involving aging of the arterial wall in addition to the formation of atheromata.

It should be emphasized that the calcific change with age in the medial elastic tissue is *not* to be confused with the gross calcareous deposits usually associated with hard and brittle plates or masses as are found in necrotic areas, Mönckeberg's sclerosis, or in long-standing intimal plaques. This elastic tissue calcification is grossly invisible and impalpable, being revealed only by methods such as microincineration or direct chemical analysis. Histologically it is usually associated with frayed and fragmented elastic fibers (6) whose staining characteristics differ from those of normal fibers. This latter problem is now undergoing further study.

TABLE 1. CALCIUM, CHOLESTEROL, AND ELASTIN CONTENT OF ATHEROMA-FREE HUMAN AORTAS

	Percentage				
Age	Medial Calcium	Intimal Calcium	Medial Cholesterol	Intimal Cholesterol	Medial Elastin
18	0.26	0.05	0.74	0.75	41.4
19	0.32	0.07	0.58	1.51	36.4
21	0.72	....	0.78	0.87	48.6
24	0.77	....	1.20	....	44.5
35	1.14	0.10	0.99	1.94	47.6
37	1.89	0.13	1.09	2.42	43.3
44	2.35	0.15	1.47	1.82	42.1
46	2.04	0.22	1.47	1.54	45.6
56	7.10	0.26	2.51	3.11	40.2
57	3.14	0.18	1.58	2.94	38.8
65	4.59	0.17	2.60	1.19	40.6
68	9.22	1.46	2.89	5.72	45.8
70	9.75	0.39	1.92	3.74	40.2
78	9.84	0.31	2.92	1.45	39.2

Analytic results for calcium, cholesterol, and elastin in an age series of human aortas free from atheromata are shown. Intimas and medias are separately analyzed. Medial calcium is calculated as percentage of dry fat-extracted elastin; intimal calcium as percentage of dry weight of intima; cholesterol as percentage of dry weight of either intima or media; medial elastin as percentage of dry, fat extracted media.

Unfortunately, there is no adequate term to describe this subtle form of calcification. For convenience, we shall use the term *elasto-calcinosis* to refer to the process whereby the normally calcium-free elastic fiber of youth is replaced by a heavily mineralized, frayed, and fragmented elastic element.

ANALYTIC SCHEME NO. 2—GRADED PLAQUE SERIES

Further information is needed on the time relations between the aging of elastic tissue and the formation of intimal plaques. While

we have shown in the preceding section that elasto-calcinosis may occur without plaque formation, the converse is not true (6). Does this imply that plaque formation is a sequel to the aging of elastic tissue?

In the human it is obviously impossible to trace the genesis of a given plaque, but it is possible to employ the method of seriation, i.e., the establishment of a series of plaques graded by severity, to infer the probable sequence of events.

It is generally agreed that the cholesterol content of a plaque is a good index of its age and severity (11). A comparison of the cholesterol contents of plaques of a graded series with the degree of elasto-calcinosis in the underlying media might indicate whether or not the development of a plaque is preceded by aging of the arterial wall.

Materials and Methods.—Our characterization of intimal lesions is in essential agreement with that of many workers (3, 11). In addition to normal tissue we collected fibrous, fatty, and grossly necrotic, ulcerated plaques. These areas were either punched out with a sharp cork borer or excised from approximately 30 aortas from individuals between 30 and 59 years of age. This age group was selected in order to cover the span which would yield both normal and severely arteriosclerotic areas. After isolating the lesion we separated intima from media (the adventitia having been previ-

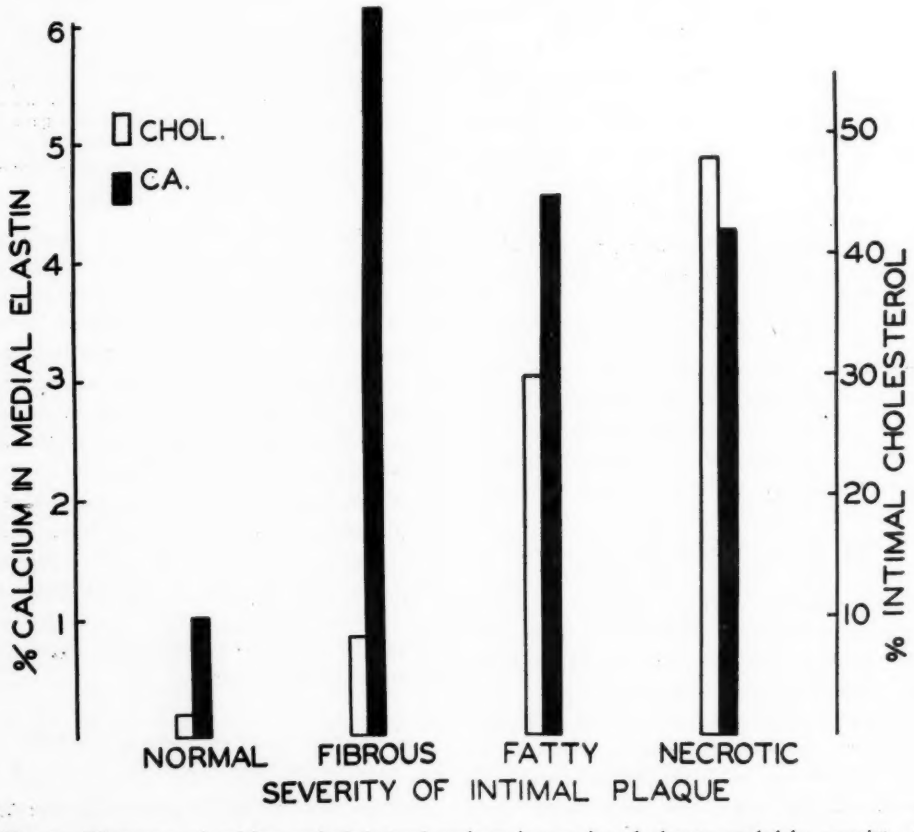

FIG. 1. Histogram of calcium and cholesterol analyses in a series of plaques graded by severity. Calcium is expressed as percentage in dry, fat-free medial elastin; cholesterol as percentage in dry intima.

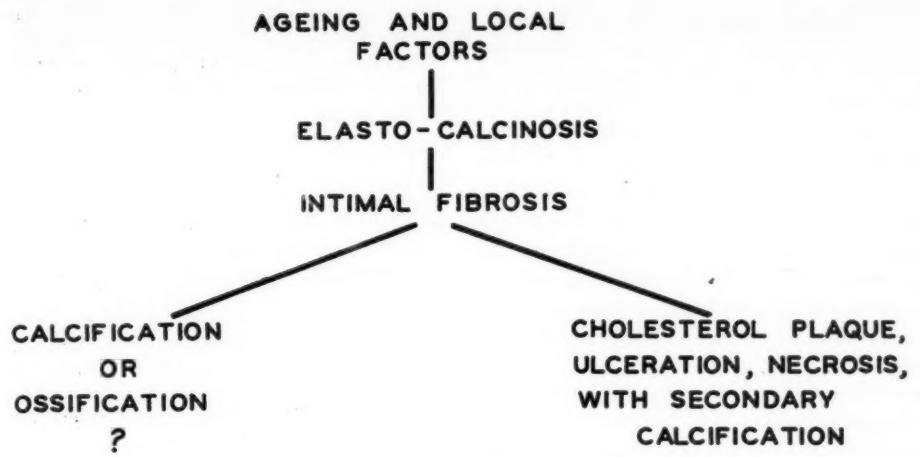

FIG. 2. Postulated sequence of events in human arteriosclerosis: a rationalization of otherwise diverse phenomena into a coordinated pattern.

ously stripped from the whole aorta) and pooled the material for analysis by the methods already described for calcium and cholesterol.

Observations.—The results obtained in this series of analyses are summarized in figure 1. They are presented as pairs of values for the calcium contents of medial elastic tissues and the cholesterol contents of the overlying intimas for the respective lesions.

Immediately apparent are two differing time sequences. That for cholesterol shows a progressive rise which reaches substantial proportions in the fatty plaques and climbs even higher in the necrotic lesions. On the other hand the degree of elasto-calcinosis leaps to a maximum immediately upon the transition from normal to fibrous intima and actually declines in the progression to fatty and necrotic plaques.

We take these facts to mean that we are dealing with a dual mechanism, consisting of two temporally and quantitatively different reactions. The elasto-calcinosis must precede the plaque formation since the calcium accumulation is associated with the transition from the normal to a fibrous lesion, whereas the cholesterol deposition becomes striking only in the later stages of atheromatosis.

DISCUSSION

Human arteriosclerosis is quite evidently complex not only in its genesis but also in its pathologic manifestations. There are usually several common variants of arteriosclerotic lesions which at first glance seem to be unrelated. Ossification may be found in the intima of the aorta without cholesterol deposits. (In the preliminary studies we have observed such ossification in at least 50 per cent of aortas from senile individuals. This lesion is being studied both histologically and histochemically and the results will be reported at a later date.) Calcification of the intima occurs with, or without, cholesterol deposition. Heavy cholesterol deposits occur in the intima without intimal calcification (11). (This last variant is generally considered to be pathognomonic for arteriosclerosis and has received further emphasis by the recent findings of Gofman and his associates (2)). Finally, intimal fibrosis occurs frequently without deposition of either cholesterol or calcium in the intima (9).

These variants of intimal plaques are now shown to be associated with and most probably preceded by elasto-calcinosis.

The introduction of elasto-calcinosis as a stepping stone to intimal plaque formation still

leaves unresolved some fundamental questions. What special factors in addition to aging are involved in the production of elasto-calcinosis? Intimal plaques do not arise uniformly in all vessels even if anatomically similar (e.g., the aorta and pulmonary artery); nor do they occur uniformly within the length of a given vessel. The variable intensity and distribution of elasto-calcinosis may be reflected in the concept developed by Moschcowitz (9) to the effect that intra-luminal pressure coupled with aging are critical factors in the genesis of arteriosclerosis.

The essence of our views may be represented by the scheme shown in figure 2.

We have indicated intimal fibrosis (hyperplasia) as the bridge between elasto-calcinosis and atheromatosis. How does this medial degeneration provoke proliferation of connective tissue in the intima? While in this paper we have stressed elasto-calcinosis as the commonest form of medial degeneration leading to atheromatosis, it should be borne in mind that other medial lesions, such as in syphilitic aortitis, are equally effective.

Summary

Arteriosclerosis is described as a dual process involving primarily an aging of the arterial wall. New observations are offered which show that calcification of senescent elastic tissue in the media (elasto-calcinosis) occurs with or without atheromatosis. When the two coexist, analyses indicate that cholesterol accumulates in the intimal plaque *after* the subjacent media has undergone elasto-calcinosis.

We wish to express our appreciation to the staff of the Snodgras Laboratory of the City Hospitals of St. Louis and to Dr. John J. Connor, Chief Pathologist, Office of the Coroner, City of St. Louis, for their generous cooperation in procuring material for these studies.

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Cytochemical Studies of Age Pigments in the Human Heart

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IN THIS INVESTIGATION DR. JAYNE DEMONSTRATES THAT AN ACID-FAST, INSOLUBLE PIGMENT, WHICH ACCUMULATES PROGRESSIVELY WITH AGE, IS FIRST FORMED AT THE POLES OF THE CARDIAC MUSCLE NUCLEI DURING THE SECOND DECADE OF LIFE. THIS PAPER WAS PRESENTED IN PART AT THE MEETING OF THE ASSOCIATION OF ANATOMISTS IN PHILADELPHIA, APRIL 13-15, 1949.

SOME of the pigment granules found in various animal tissues have been thought to owe their origin to the process of aging. This assumption seems to be justified since pigments are not normally found in young animals but are seen in the tissues of old animals.

Many such observations have been made during the last fifty years, but the evidence is far from conclusive. Hodge (9) observed over half a century ago in honey bee and human nerve cells that there is a pronounced increase with age in the amount of pigment granules present. Later Mühlmann (17) stressed the significance of pigmentation of nerve cells with age. According to Connor (3) two groups of pigments accumulate in the body with age, namely lipochrome and hemofuchsin (with hemosiderin). The former of these is exogenous in origin and is found normally in such organs as the adrenal cortex, corpus luteum, liver, spleen, and skin. Hemofuchsin is the "wear and tear" pigment and has been found in many organs, including the heart.

Although a variety of pigments are frequently found and are widely distributed, little is known about their exact chemical nature. Moore and Wang (16) seem to have conducted the only investigations in this respect. They attempted to analyze the brown fluorescent pigment which accumulated in the tissues of rats reared on a diet deficient in vitamin E. Previously a number of investigators had found that rats deprived of vitamin E developed pigmentation of smooth muscle and other tissues (Barrie, 1; Evans and Emerson, 5; Hessler, 8; Mason and Emmel, 12; Martin and Moore, 14 and 15). The results of Moore and Wang's (16) analyses led them to conclude that the brown fluorescent pigment probably arises from abnormal oxidation of protein, and the presence of oxidized and deaminated groups derived from tryptophane was suspected. According to these authors this pigment separated from the vitamin E deficient rat tissues possesses many of the chemical properties described for hemofuchsin derived from the human intestine.

In reviewing the literature on pigmentation the terminology which has been introduced by writers on this subject is often perplexing. In order to avoid further confusion some of the variations in designation and classification of pigments are listed:

Lipochrome: Most German writers believed this to be wear and tear pigment and therefore endogenous in origin. Willstätter and Escher (23) and Escher (4) believed lipochromes consist of carotene and xanthophyll and that they are exogenous in origin. Lison (11) considered that lipochromes consist of chromolipids and carotinoids.

Chromolipids: According to Palmer (18) chromolipids consist of carotene and xanthophyll.

By the application of methods previously described and by chemical examinations, Connor (3) listed and characterized 5 pigments as follows (hereafter the terminology used in this paper will conform to Connor's classification):

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(a) Melanin is intensely blackened by silver nitrate, is insoluble in acids, alkali, and fat solvents.

(b) Hemosiderin (wear and tear pigment), an iron-containing pigment, is insoluble in fat solvents, may be darkened with silver nitrate, stains irregularly with fat stains, and is lightly stained with basic fuchsin.

(c) Hematoidin is soluble in tissue fluids, darkened with silver nitrate, contains no iron, and does not stain with fat or basic dyes.

(d) Hemofuchsin (wear and tear pigment) is insoluble in fat solvents, but partly soluble in alkali, does not give the iron reaction, darkens with silver nitrate, and stains lightly with fat stains.

(e) Lipochrome (carotene, xanthophyll) is associated with fat, does not stain with fat stains, is soluble in fat solvents, and darkens with silver nitrate.

Because of the wide gaps in our knowledge of age pigmentation, these experiments were undertaken to determine the relationship of human heart pigment to age and characterize the human heart pigment cytochemically.

Material and Methods

One hundred and thirty-five human hearts of different age groups (5 days to 89 years of age) were obtained two to four hours post mortem. The causes of death classified according to category of disease and age group are listed in table 1.

The area selected for study was the myocardium near the apex of the left ventricle which was excised and fixed in alcohol-formalin. After fixing for twenty-four hours the tissues were dehydrated, cleared in cedar-wood oil, and embedded in paraffin. Sections 5 μ thick were stained for twenty-four hours in Verhoeff's carbol-fuchsin at 58 C., then destained for three hours with 3 per cent hydrochloric acid in 70 per cent alcohol. After washing thoroughly with water the sections were routinely counterstained with Harris' hematoxylin and mounted in clarite.

Separation of Pigment Granules.—The granules were separated according to the following

Table 1. Causes of Death Classified According to Category of Disease and Age Groups

Age Group	Total Number of Specimens	Chronic Infections	Acute Infections & Inflammations	Malignant Diseases	Cardio-Vascular Diseases[1]	Renal Diseases	Miscellaneous Diseases
5 days–10 years	23	0	8	1	2	0	12
11–20 years	9	7	1	0	1	0	0
21–30 years	23	11	4	3	5	0	0
31–40 years	19	3	11	4	1	0	0
41–50 years	17	0	1	6	10	0	0
51–60 years	19	4	1	6	8	0	0
61–92 years	25	1	2	5	17	0	0
Total	135	26	28	25	44	0	12

[1] In this category no distinction has been made between chronic cardiovascular disease (such as long-standing rheumatic heart disease with terminal failure) and acute terminal cardiovascular disease such as coronary occlusion.

procedure: 30 Gm. of muscle, 2 Gm. of pepsin (Merck U. S. P.), and 100 cc. distilled water were blended for thirty minutes in a Waring blender. After the acidity was adjusted to a pH value of 4.5 by the addition of hydrochloric acid the suspension was placed in an oven at 36 C. At the end of forty-eight hours the pH was readjusted to 6.7, 2 Gm. of trypsin (Merck U. S. P.) were added, and the flask was put back in the oven at 36 C. for another forty-eight hours.

In order to extract the lipids, 100 cc. of chloroform were added and the mixture was refluxed for a period of twelve hours. Upon standing in a separatory funnel for twenty-four hours at room temperature three distinct layers were formed. Since the middle zone contained most of the granules which had been set free by previous treatment, the remaining layers were discarded. The solution with suspended granules was centrifuged for ten minutes at 2000 r.p.m. and the supernatant fluid discarded, leaving the granules and some debris, the latter being impossible to remove even after repeated washings.

Solubility Tests on the Isolated Granules.—Tests for solubility were made (a) in strong acids (concentrated hydrochloric, 6 N hydrochloric, concentrated sulphuric, 6 N sulphuric, and a mixture of equal parts of nitric acid, hydrochloric acid, and water), (b) in alkalis (5 per cent sodium hydroxide, and in 0.1 N sodium hydroxide), the sample in all cases being kept in sealed tubes at 105 C. for two days, and (c) in the usual fat solvents (alcohol-ether, acetone, benzene, carbon disulfide, dioxane, isobutanol, and toluene) kept at room temperature for a period of thirty-five hours.

Cytochemical Procedure.—The granules were analyzed for inorganic (ferrous and ferric) and organic iron according to the methods outlined by Glick (6). For detection of lipids, formalin fixed frozen sections were stained with sudan III and Tarao's (22) protease-nile blue sulphate for bound lipids; for cholesterol the Liebermann-Burchard reaction as adapted for histologic purposes by Schultz was employed. Other diagnostic procedures used included Millon's test for protein and methyl green stain for "ceroid" (Lillie, Daft, and Sebrell, 10).

Results

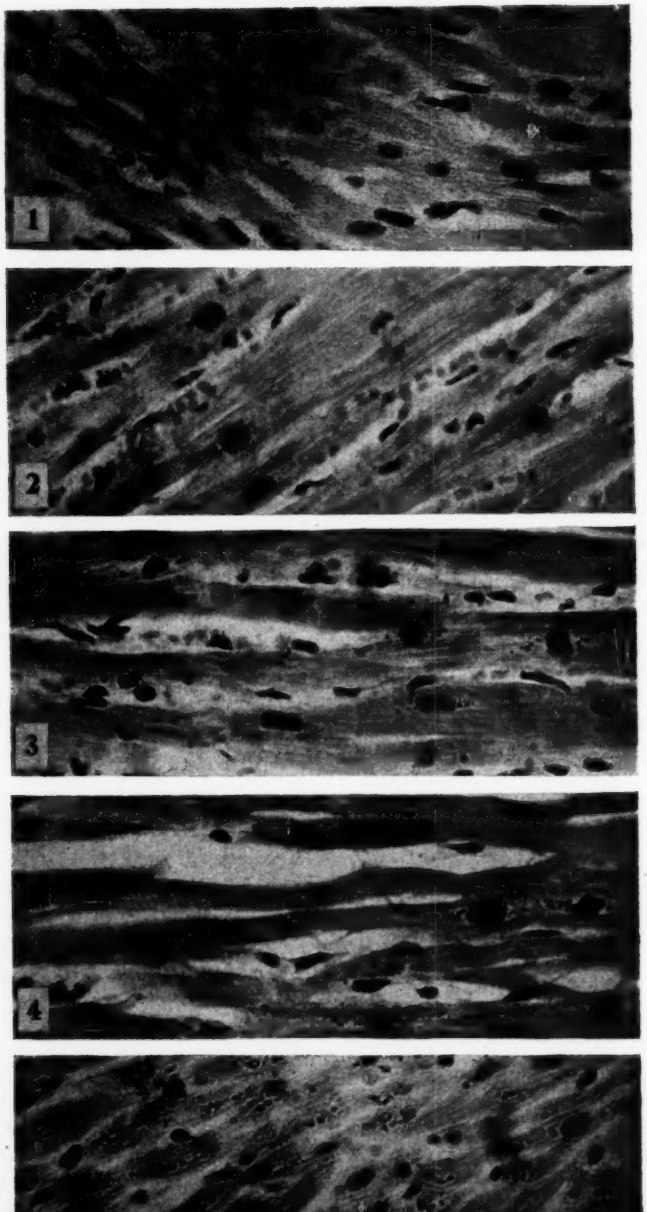
Histologic Observations.—Beginning about the second decade of life the muscle fibers begin to show definite morphologic changes (fig. 2). These changes are made evident by the loss of transverse striation, vacuolation, and reduced affinity for dyes at the nuclear poles. In conjunction with or following these changes golden brown pigment appears as single granules or as small clusters of granules at either or both poles of the nuclei (fig. 2). In older specimens the granular aggregates become heavier, extending distally from the nuclear poles but appearing also in other areas of the muscle fiber (figs. 3-5). The amount, granular size, and distribution of the pigment are somewhat variable among different cells, even of the same section.

In routinely hemotoxylin and eosin stained sections the eosin usually masks the pigment to a greater or lesser extent. In carbol-fuchsin stained sections the granules retain the red dye even after a prolonged period of acid-alcohol differentiation.

As shown in table 2 pigment was present in the muscle cells in only one of the 23 specimens under 10 years of age. However, in the second decade only one of a total of 9 specimens failed to show the presence of at least a small amount of pigment. All of the specimens examined which fell into the older age groups (21 years and older) contained variable amounts of pigment granules.

Although exact quantitative evaluation was not practical, results of attempts to correlate the amount of pigment occurring in the cardiac muscle with age indicate that, in general, pigmentation increases with age with respect to both the number of cells affected and the concentration per cell (figs. 2-5).

Approximately half of the cells were pigmented in those specimens 20 years of age or younger which contained pigment (fig. 2). In



HEART, Verhoeff's carbol-fuchsin and Harris' hematoxylin. X470.

TABLE 2. ESTIMATED AMOUNT OF PIGMENT BY AGE GROUPS

Age Group	Number of Females	Number of Males	Average Relative Amount of Pigment[3]
5 days–10 years[1]	10	13	0
11–20 years[2]	5	4	+
21–30 years	12	11	+++
31–40 years	10	9	++
41–50 years	7	10	+
51–60 years	10	9	+++++
61–92 years	10	15	+++++

[1] Only one of this group contained pigment.
[2] Only one of this group did not contain pigment.
[3] The symbols 0, +, etc. refer to the estimated degrees of pigment deposition in the specimens examined. See figures for evaluation as follows: 0 - fig. 1, + - fig. 2, +++ - fig. 3, ++++ - fig. 4, +++++ - fig. 5.

half the specimens of the third decade about 95 per cent of the cells were pigmented, while in the remaining specimens roughly 50 per cent of the cells were so affected. A greater percentage of cells were pigmented in the older age groups (30 years and older) than in the younger age groups and in the former there was more individual variation in pigment concentration per cell than in the latter.

Chemical and Histochemical Observations.—About half of the final product obtained by the digestion procedure consisted of pigment granules which apparently had not been affected by the reagents used. Further tests revealed that the free granules are insoluble in acids, alkali, and the usual fat solvents (table 3). Results of the histochemical tests are also tabulated in table 3.

TABLE 3. SOLUBILITY AND CYTOCHEMICAL TESTS

Reagent (or Test)	Result
1. HCL, concentrated	Insoluble
2. 6N HCL	Insoluble
3. H_2SO_4, concentrated	Charred
4. 6N H_2SO_4	Insoluble
5. Equal Parts HCL, HNO_3, H_2O	Insoluble
6. 5% NaOH	Insoluble
7. 0.1N NaOH	Insoluble
8. Fat Solvents (see text)	Insoluble
9. Iron (organic and inorganic)	Negative
10. Sudan III	Questionable
11. Osmic Acid	Granules Black
12. Nile Blue Sulphate	Granules Greenish Blue
13. Liebermann–Burchard Reaction	Negative
14. Fuchsin Sulphurous Acid (Thymonucleic Acid)	Negative
15. Millon's Test	Granules Dark Red
16. Methyl Green	Granules Not Stained

DISCUSSION

It is apparent from table 2 that pigmentation of the cardiac muscle increases progressively with age. The individual variation in amount of pigment in specimens of the same age may possibly be accounted for by disease and dietary variations. In the condition known as hemochromatosis, hemofuchsin, an iron-free pigment, was found in the smooth musculature of the stomach and intestine (Recklinghausen, 21). Brown pigment which did not stain for iron was found also in the heart (Opie, 20) and intestinal musculature (Blaschko, 2; Goebel, 7) of aged human subjects. Recently Pappenheimer and Victor (19) found an acid-fast, insoluble pigment in the liver and other organs of humans who died from diseases involving chronic intestinal disorders.

Although there is no direct evidence of the effect of vitamin E deficiency in man, Mason and Telford (13) found that monkeys reared on a vitamin E deficienct diet developed an acid-fast pigment in certain smooth muscles

FIG. 1. Apex of left ventricle of a 3 year old male. No pigment is visible.

FIG. 2. Apex of left ventricle of a 16 year old female. Striations have disappeared at the nuclear poles and pigment is beginning to accumulate.

FIG. 3. Apex of left ventricle of a 25 year old female. Somewhat more pigment is present than in fig. 2.

FIG. 4. Apex of left ventricle of a 51 year old female. Pigment extends further distally from the nuclear poles than in figs. 2 and 3.

FIG. 5. Apex of left ventricle of a 75 year old male. An extensive accumulation of pigment is present.

←

and small amounts in skeletal and cardiac muscle cells. Since the pigments obtained from the smooth muscle cells of human intestines and the smooth muscle of vitamin E deficient rats had much the same chemical properties and solubilities, Moore and Wang (16) considered these to be closely related. However, the acid-fast pigment in the human heart muscle differs from that in vitamin E deficient animals in at least four important respects. The former is insoluble in isobutanol, is insoluble in sodium hydroxyde solution, is not stained by methyl green, and does not give a positive reaction for thymonucleic acid. As mentioned previously this pigment gives a positive Millon test for tyrosine or tryptophane derivatives. The interpretation of the reaction of the granules with sudan III is complicated by the natural color of the pigment; however, they are stained greenish blue by nile blue sulphate even before treatment with proteolytic enzymes.

Connor (3) was of the opinion that these dyes and others were merely adsorbed on the surface of pigments. However, in this instance, since the pigment in the cardiac muscle is blackened by osmic acid, the presence of a lipoid is strongly suggested. The fact that the granules do react with osmic acid but do not give a positive Shultz test suggests the presence of a lipoid other than cholesterol or its esters. A possible lipoid which would have these characteristics might be an unsaturated lipoid, which in this case would be bound to a higher molecular weight protein.

Summary

1. An acid-fast pigment appears in the cardiac muscle fibers during the second decade of life and increases progressively with age.

2. The pigment separated from the heart muscle is insoluble in acids, alkalis, and fat solvents.

3. The pigment possesses many of the properties which have been described for hemofuchsin. Its properties, however, differ somewhat from those reported for the pigment which develops in tissues of animals as a result of vitamin E deficiency.

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Vitamin Studies in Middle-Aged and Old Individuals

V. Hypovitaminemia B_1 . Effect of Thiamine Administration on Blood Thiamine Concentration and Clinical Signs and Symptoms

MARGARET CHIEFFI AND JOHN ESBEN KIRK

IN AN INVESTIGATION OF 20 ELDERLY PATIENTS WITH LOW BLOOD THIAMINE VALUES, TREATMENT WITH 5 MG. OF THIAMINE HYDROCHLORIDE BY MOUTH WAS FOLLOWED BY A BENEFICIAL EFFECT ON EXISTING EDEMA OF THE LEGS AND TENDERNESS OF THE CALVES. THE THIAMINE TREATMENT ALSO RESULTED IN THE ATTAINMENT OF NORMAL THIAMINE BLOOD VALUES.

IN a previous investigation (3) a comparison was made of the incidence of occurrence of 54 symptoms and signs in a group of old individuals with low (0-2.0 micrograms per cent) and with normal (3.5-6.0 micrograms per cent) thiamine blood levels. A review of the findings showed that edema of the legs, tenderness of the calves, impairment of the vibratory sense of the lower extremities, localized subconjunctival thickening, and redness and fissures of the tongue occurred with significantly greater frequency in the subjects with hypovitaminemia B_1 than in the control group.

Although the first three of these symptoms and signs correspond well to those generally accepted as being characteristic of thiamine depletion, the subconjunctival thickening and changes of the tongue have not generally been associated with uncomplicated thiamine deficiency and might be assumed to be caused by a concomitant lack of other nutritional factors. In order to elucidate further the significance of the clinical findings it was decided to treat the B_1-hypovitaminemic patients with thiamine and to evaluate the response to such administration. Disappearance or amelioration of the clinical signs following thiamine treatment would confirm the assumption that they were manifestations of thiamine deficiency.

EXPERIMENTAL

Twenty old patients who in the previous investigation had been found to have blood thiamine concentrations below 2 micrograms per cent were selected for study. Immediately before the thiamine treatment was started the blood thiamine values were again determined and it was ascertained that all the patients still had values below 2 micrograms per cent. The mean thiamine concentration at the commencement of therapy was 1.8 micrograms per cent. The mean age of the patients was 74 years (range 54 to 101 years).

The blood thiamine determinations were performed by the method of Friedemann and Kmieciak as described in a previous communication (2).

Five mg. of thiamine hydrochloride were given daily by mouth for fifteen weeks. The thiamine was given in tablet form in a single dose and the administration was supervised by a nurse.

During the period of vitamin therapy, thiamine blood determinations and clinical examinations were performed at intervals of from two to four weeks. After discontinuation of the treatment the examinations were repeated at longer intervals for a period of six months.

RESULTS

The effect of the oral administration of thiamine hydrochloride on the mean blood thiamine concentration of the individuals is

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Dr. Kirk is Associate Professor of Medicine and Director of Research, Division of Gerontology, Washington University School of Medicine. He received his M.D. degree in 1929 from the University of Copenhagen and was certified as a specialist in internal medicine (1938) and clinical pathology (1948). From 1931 to 1934 Dr. Kirk was assistant resident physician at the Rockefeller Institute. From 1936 to 1939 he was on the staff of the medical university clinic and director of the City Laboratories, Copenhagen. From 1939 to 1947 he was chief physician at the medical service, Holstebro County Hospital, Denmark.

His primary fields of research have been in clinical medicine and biochemistry. He is a member of the American and Danish Gerontological Societies and the Danish Society of Internal Medicine, a member of the Harvey Society, and a Fellow of the Royal Society of Medicine, England.

shown in figure 1. The treatment, within two weeks, produced a rise to normal values (4 to 5 micrograms per cent), and a maximal concentration was reached after ten weeks. Following discontinuation of treatment there was a decline in the mean blood thiamine concentration with a return to the initial level in 6 months.

The effect of thiamine treatment on the edema of the legs, loss of vibratory sense of the lower extremities, and tenderness of the calves is shown in figure 2. Prior to treatment 15 of the 20 patients under investigation presented edema of the lower extremities. The edema was not associated with other clinical symptoms or signs of circulatory failure (cyanosis, dyspnea, distention of cervical veins, pulmonary hypostases, enlargement of the liver or ascites) and was not hypoproteinemic in origin since the plasma protein values in all the edematous subjects were normal (total protein 7.37 Gm. per cent, range 6.56 to 8.09; albumin 4.49 Gm. per cent, range 3.82 to 4.88; globulin 2.87 Gm. per cent, range 2.19 to 3.37). After three weeks of thiamine supplementation the edema had disappeared in 10 of the patients, and in only 2 did edema persist after fifteen weeks of treatment. Six months after discontinuation of thiamine therapy 10 of the patients again presented edema of the legs.

Four subjects complaining of tenderness of the calves were all relieved after three weeks' treatment and in 3 the symptom recurred following discontinuation of thiamine.

Impairment of the vibratory sense of the lower limbs was found in 5 patients. Of these, 3 improved after three weeks' thiamine therapy, and at the completion of the fifteen weeks' treatment 4 had regained normal sensation. In only one of these patients did the symptom return following the suspension of treatment.

The effect of thiamine supplementation on subconjunctival thickening and redness and fissures of the tongue is shown in figure 3. Twelve patients exhibited subconjunctival thickening prior to thiamine administration. Of these only 2 improved during thiamine supplementation and in neither of these subjects did the symptom recur when the vitamin was discontinued.

In 2 of 3 patients presenting fissures of the tongue, three weeks' thiamine treatment resulted in disappearance of the fissures. In both cases the fissures returned when the thiamine therapy was suspended.

Five patients had redness of the tongue prior to treatment. In 3 the redness disappeared after three weeks' thiamine administration, and in all the individuals the tongue had become normal after ten weeks' treatment. Following suspension of thiamine the redness of the tongue recurred in all 5 patients.

All the 20 patients treated with thiamine spontaneously commented on an increase in appetite which they noted shortly after the

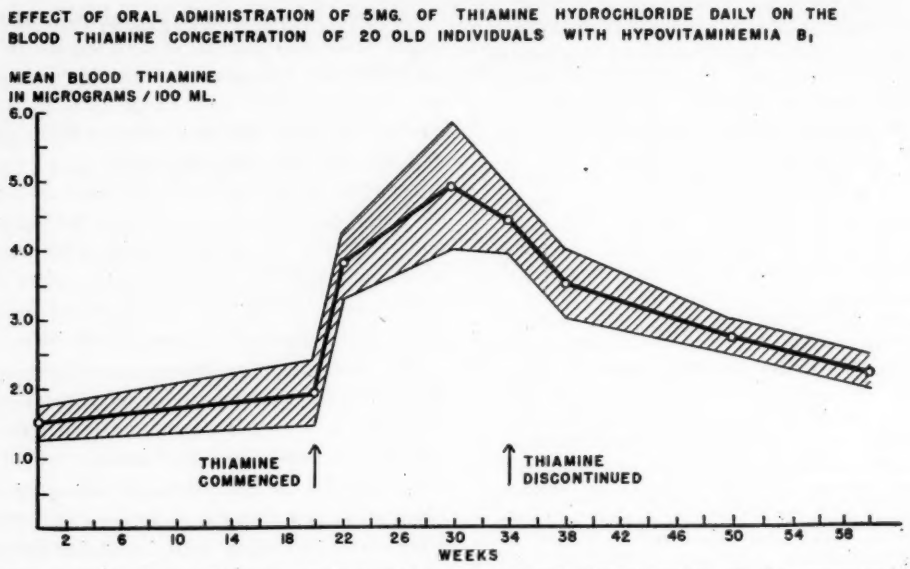
EFFECT OF ORAL ADMINISTRATION OF 5MG. OF THIAMINE HYDROCHLORIDE DAILY ON THE BLOOD THIAMINE CONCENTRATION OF 20 OLD INDIVIDUALS WITH HYPOVITAMINEMIA B1
MEAN BLOOD THIAMINE IN MICROGRAMS / 100 ML.
6.0
5.0
4.0
3.0
2.0
1.0
THIAMINE COMMENCED
THIAMINE DISCONTINUED
2 6 10 14 18 22 26 30 34 38 42 46 50 54 58
WEEKS

FIG. 1. The effect of thiamine administration and subsequent discontinuation on the concentration of thiamine in the blood. (The shaded area represents ± 0.5 s.d.)

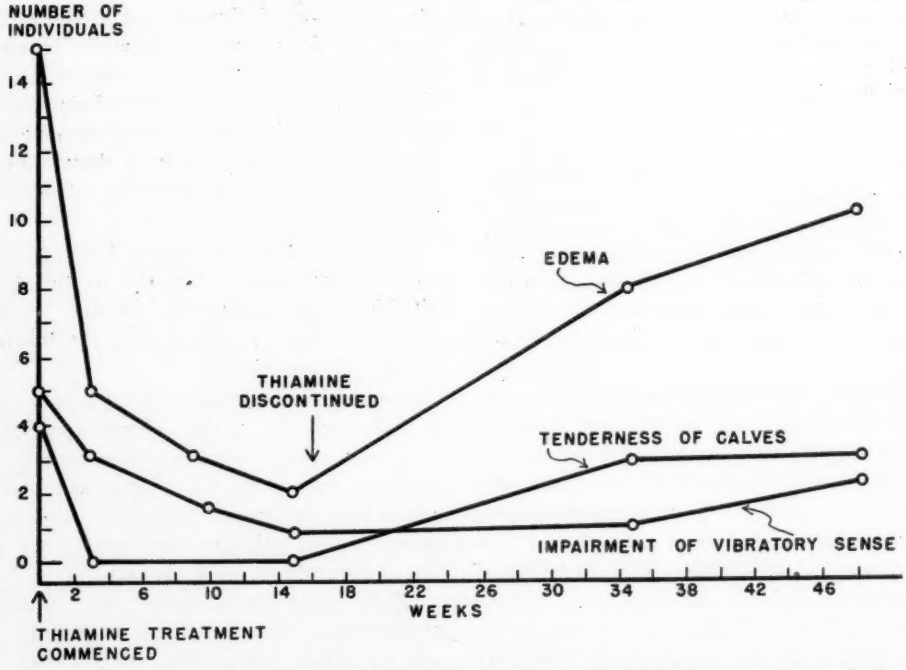

FIG. 2. The effect of thiamine administration and subsequent discontinuation on edema of the legs, tenderness of the calves, and impairment of the vibratory sense.

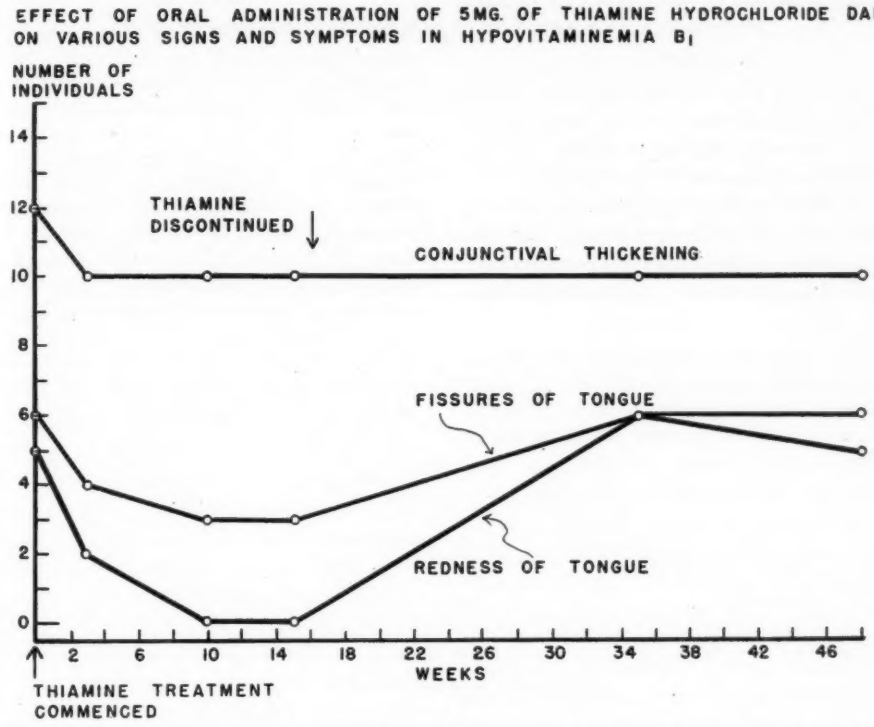

FIG. 3. The effect of thiamine administration and subsequent discontinuation on conjunctival thickening and redness and fissures of the tongue.

therapy was commenced. A moderate gain in weight was observed in all the patients during the fifteen weeks' treatment, the mean increase being 2.0 Kg.

DISCUSSION

The contention that thiamine deficiency was responsible for certain of the signs and symptoms found in our patients with hypovitaminemia B_1 received confirmation from the beneficial results of thiamine therapy. That such improvement was a direct result of the vitamin B_1 administration is supported by the observation that the pathologic states recurred following the suspension of thiamine supplementation.

In the group of patients studied, edema of the legs and tenderness of the calves were the two findings most responsive to thiamine therapy.

The improvement following thiamine supplementation in all of 5 patients presenting redness of the tongue was an unexpected finding since this sign has not been commonly described as a manifestation of vitamin B_1 deficiency. In the Elgin State Hospital study (4), however, a case is reported of a severe tongue lesion produced by deprivation of the B-complex vitamins, which improved markedly after a few days of thiamine administration.

Although subconjunctival thickening was a frequent finding in the B_1 hypovitaminemic patients, the lack of response to the administration of the vitamin would indicate that thiamine was not the factor involved. Previous studies by us (1) have shown that the conjunctival thickenings in old patients frequently are found

in association with low plasma levels of vitamin A.

Summary

The results of peroral administration of thiamine hydrochloride over a fifteen week period in a daily dose of 5 mg. to 20 elderly individuals with hypovitaminemia B_1 is reported. The effects on the thiamine blood level and on various signs and symptoms were noted. The observations were continued for six months after the discontinuation of the thiamine supplementation.

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Investigations of the Actual Food Intake of Elderly Chronically Hospitalized Patients

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MEASUREMENTS OF THE ACTUAL FOOD INTAKE OF 20 DEBILITATED PATIENTS DISCLOSED THAT ALTHOUGH AN ADEQUATE DIET WAS OFFERED MOST OF THE PATIENTS CONSUMED AN INSUFFICIENT AMOUNT OF CALORIES AND SPECIFIC NUTRIENTS.

ONE of the main problems with which the speciality of geriatrics is confronted is the question of the importance of nutrition for a healthy old age. This problem has so far not been the subject of intensive studies.

Whereas acute deficiency diseases such as pellagra, beriberi, and scurvy are reported to occur only infrequently with advancing years (Ohlson, Roberts, Joseph, and Nelson, 11), the chronic deficiency states seem to be of etiologic significance for many diseases in old age. Thus deficiency of calcium, phosphorus, and vitamin D are considered as etiologic factors in the development of osteomalacia, and lack of iron in the causation of hypochromic anemia.

Various investigations further indicate the frequent occurrence of protein deficiency in old individuals. It is furthermore often believed that a number of symptoms which are generally ascribed to old age as such in reality are caused by a hypovitaminosis. The importance of a chronic vitamin deficiency in the causation of such symptoms as tiredness, anorexia, debilitation, and neuroses is as yet unknown in spite of the possible considerable significance of an adequate vitamin intake for rehabilitation of old patients. Tuohy (19) estimates the frequency of the latter symptoms in patients above 60 years of age to be at least 33 per cent and is of the opinion that an adequate nutrition constitutes the main chance of these individuals to regain their lost vitality.

A number of factors are present which contribute to the frequency of subnutrition in this age group. "Hunger lessens as age advances" (Tuohy, 19), a fact which is most often explained as a consequence of the decreased basal metabolic rate with advancing years (Du Bois, 5) and the reduced muscular activity. Simultaneously with the decreased caloric intake the ingestion of specific foods is lowered, for which the requirement is hardly reduced in proportion to caloric needs. Unfavorable economic conditions also result in a shift from more expensive to cheaper and less valuable foods. The main source of calcium and lactoflavin is milk, and this food is for unknown reasons often replaced by other beverages (11).

A poor condition of the teeth or inadequate dentures would often be responsible for the elimination from the diet of foods such as meat and vegetables which require mastication, or the food is cooked longer and the loss of vitamins is increased. Old men who on the loss of their wife suddenly are confronted for the first time with the task of doing the cooking often resign themselves to ingestion of poorly prepared and little varied foods, and the loneliness itself and the lack of company at the meals tend to lower the standard for the esthetic preparation of the food. Finally, in senile dementia the interest in food is frequently reduced or absent.

Among the patients in the hospital De Gamles By in Copenhagen the symptoms of glossitis, cheilosis, and perlèche are found with great frequency, signs which are usually attributed to deficiency of B vitamins and/or iron.

In order to investigate the nutrition of the patients with such symptoms we have measured the actual daily intake not only of iron and of certain of the B vitamins but also of the other constituents of the diet.

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Experimental

Group of Patients Studied.—The food survey was made on 20 patients, 16 women and 4 men, in the department for chronically debilitated patients in De Gamles By. The patients were either confined to bed or were wheel chair cases. None of them suffered from acute diseases during the period of investigation. All the patients had increased redness and papillary atrophy of the tongue and/or cheilosis, the latter condition consisting of increased redness of the lips, desquamation, atrophy of the mucous membrane, or ulcerations in the angles of the mouth (perlèche). The further clinical data for the patients are given in table 1. As mentioned previously, all the patients included in the study presented signs of generalized or focal glossitis. The incidence of these symptoms among the patients in the hospital as a whole was 30 per cent.

Method of Food Evaluation.—The composition of the food was examined by weighing or measuring all the constituents for 2 one week periods before the onset of the main investigation. Care was taken that the food portions served during this preliminary period were the same as during the investigation itself. The measurements of the portions took place without the knowledge of the patients so that eventual psychologic effect on the appetite was eliminated. Any supplement to the hospital foods in the form of fruit, candy, and cakes was registered by the nurses and was included in the calculations. The quantities of ingested foods were recalculated as to actual constituents on the basis of the food preparation employed by the kitchens and were subsequently expressed as calories, protein, calcium, phosphorus, iron, vitamin A, thiamine, riboflavin, nicotinic acid, and vitamins C and D by the use of food tables (Ege, 6). In these calculations the seasonal variations of vitamin A and C contents of various foods were considered. No correction was made for the loss incurred in the cooking, whereas the calcium binding property of phytin was considered.

Results and Comments.—In table 2 the average daily intake of calories, protein, calcium, phosphorus, iron, vitamin A, thiamine, riboflavin, nicotinic acid, ascorbic acid, and vitamin D is recorded for the 20 patients.

Calories.—It is a well established fact that the basal metabolic rate decreases with advancing years. For women above 60 years of age the basal metabolism for a person of 65 Kg. body weight is about 1300 calories (Brody, 3). If to this figure 10 per cent is added representing the specific dynamic action of the proteins, and if the minimal muscular activity which old people of our category perform is estimated to 150 calories for twenty-four hours, a total metabolism of 1600 calories is obtained.

It will be seen from table 2 that the mean caloric intake for the patients in our study was only 1037 calories for the women and 1332 for the men and that in all the patients the caloric intake was considerably below the value of 1600 calories estimated above.

A very low caloric intake in old women has previously been reported by Ohlson (11), who in a study of the dietary habits of old individuals observed that failing health constantly was associated with a reduced intake of food. A chronically low caloric intake is, however, neither a specific nor constant finding in old age; thus Winters and Leslie (22) also noted an insufficient caloric intake in poor middle-aged women, whereas on the other hand Pyke, Holmes, Harrison, and Chamberlain (15) found a caloric intake between 1450 and 1700 calories in 11 out of 12 women in a small institution for old people.

In the present study the body weight of the patients was in several instances redetermined three months after the dietary studies had been

completed. In those instances in which the food intake during these three months was of the same order of magnitude as in the experimental period the body weight was found to be stationary on caloric intakes between 900 and 1250 calories, so the calculated caloric intake can be considered equal to the total metabolism.

It is a question whether a metabolism of 1000 calories per twenty-four hours can be considered as physiologic for these inactive patients or whether it is a pathologic phenomenon. In the latter case the low metabolism might be regarded as a consequence of subnutrition and thus of a nature similar to the reduction in metabolic rate observed in the more acute conditions of anorexia.

Concerning the effect on the organism of a caloric intake of about 1000 calories daily over a period of several years nothing definite is known. It is possible that a compensatory adjustment of the metabolism to a lower level takes place and that the muscular inactivity which was a predominant finding in several of our patients is the result of the subnutrition. That on the other hand a decreased vitality may have induced the insufficient food intake is very probable, which suggests the possibility of the existence of a vicious circle between chronic subnutrition and reduced activity.

Protein.—The average intake of protein for the 16 women was 29 Gm. per day, ranging between 43 and 20 Gm.; for the men the mean value was 38 Gm.

The requirement of protein in old age is usually reported to be of the same magnitude as in middle-aged persons. A positive nitrogen balance in old individuals was observed by Owen, Irving, and Lyall (13) on 0.87 Gm. of protein per kilogram of body weight and by Adams, Boothy, and Snell (1) on 1.2 Gm. On the basis of these data a daily intake of 1 Gm. of protein per kilogram of body weight may be accepted as adequate.

As mentioned previously the protein intake in several of the 20 patients included in this study was less than half of this figure. With such a low intake it does not appear unlikely that a negative nitrogen balance may develop. In this connection it should be mentioned that Bock (2) observed reduced serum protein values in apparently healthy old individuals over 80 years of age and that Pietra (14) by administration of a protein-rich diet in the form of artificial protein preparations to 15 old patients succeeded in returning reduced protein values to normal.

Calcium and Phosphorus.—In all but 2 cases the calcium intake in the present study was found to be considerably below 0.6 Gm. per day, the generally accepted norm for middle-aged adults. The phosphorus intake in all the patients was below the recommended allowance of 1.3 Gm. The absolute calcium intake varied between 0.19 and 0.65 Gm. (mean 0.34 Gm.) and the phosphorus intake between 0.44 and 0.86 Gm. (mean 0.57 Gm.).

As will be seen from table 2 no great correlation was observed between the caloric intake and the calcium ingestion. Thus patients V. K. and K. H. received an amount of calcium close to the recommended norm but in these individuals the caloric intake was considerably reduced. Both patients obtained the main part of the calcium supply through three glasses of milk and 20 Gm. of cheese daily. The reason the calcium intake was so low in the majority of the other patients was the low milk consumption. Each morning and evening the patients were given the choice between tea, milk, and beer, and most of them preferred tea or beer. Thus 65 per cent drank no milk at all, 30 per cent drank one-half to one glass daily, and only 5 per cent two glasses daily. A wide-spread cause for refusal of milk seems to be the general conviction of the Danish population that milk produces constipation. Some refused milk because they preferred the taste of beer.

In balance studies performed on old individuals Owen (12) found the requirements in old age the same as in young individuals and is of the opinion that the insufficient intake of calcium of old persons is no more harmful than in young subjects. Whether the senile

osteomalacia is conditioned by an endocrine disturbance or is caused by an insufficient calcium intake alone will not be discussed in detail here. From the data presented in this study and in Owen's publication it will, however, seem reasonable to conclude that an insufficient calcium intake in itself may be a sufficient explanation for the decalcification of the bone system.

Iron.—In all the subjects studied the daily iron intake was considerably below the generally accepted standard of 12 mg. per day. The intake varied between 3.2 and 9.2 mg. with a mean value of 4.5 mg.

The frequency of occurrence of iron deficiency anemia in old subjects living alone is not known, but a study of this problem is in progress. In the present group of patients, in spite of the low iron intake, anemia was present in only 35 per cent (hemoglobin percentage below 80). It is of course possible that sideropenia existed in the other patients too. Thus the hemoglobin values in the remaining 65 per cent of the patients were at the lower limit of normal, and as shown by Waldenström (20) sideropenia may exist with a normal hemoglobin content. On the basis of serum iron determinations Waldenström (20) finds that sideropenia is a rather frequent disease in old age.

Vitamin A.—The vitamin A intake of the women was in all instances below the recommended intake for middle-aged persons of 2500 units per day; for the men the intake was close to this value.

The observed mean values of 1395 units for the women and 2052 units for the men correspond fairly closely to those found by Pyke (15) in old women on a freely selected diet, in spite of the fact that the patients in Pyke's group had a considerably higher caloric intake. It can be calculated that if the mean caloric intake of our patients had been 2100 calories the vitamin A consumption would have been 2800 units or, in other words, the diet would have been sufficient with regard to vitamin A. The relative high vitamin A content in the diet is due to the serving in the hospital of vegetables at least once weekly and to the enrichment of oleomargarine with vitamin A required in Denmark.

Thiamine.—Out of the 20 patients included in this study none received an amount of thiamine which even approached the recommended dose of 1.2 mg. daily, and only 3 patients received more than 0.6 mg.

Rafsky and Newman (17) in saturation experiments with thiamine observed that a larger dose was required in order to obtain saturation with this vitamin in old persons than in young subjects. Judging from the low intake of thiamine by the patients in the present study a considerable possibility for the development of a deficiency should exist, unless the requirement of old individuals is lower than that of young subjects. Observations by Mills (10) are, however, against such an assumption, since Mills on the contrary found a higher optimum for old than for young rats.

Riboflavin.—Only 1 of the 20 patients in the investigation consumed an amount of riboflavin corresponding to the recommended dose for adults of 1 to 2 mg. The mean riboflavin intake was 0.7 mg. As was the case with the calcium consumption the riboflavin intake was found to depend nearly exclusively on the milk ingestion. Only the one patient who drank two glasses of milk daily received sufficient riboflavin.

In 1947 Daubenmerkl (4) in an investigation of a large group of old patients in De Gamles By reported a definitely lower excretion of riboflavin, both spontaneously and in load tests, in the old individuals than in the control material of younger employees, and clinical observations by Lundh and Geill (9) in 1942 showed that administration of riboflavin in daily doses of 5 to 30 mg. to patients with cheilitis and dysphagia was followed by a disappearance of these symptoms.

The existence of a high incidence of aribo-flavinosis among the patients in the hospital is consistant with the observed minimal milk intake and emphasizes the importance of urg-

ing old individuals to drink milk daily in an amount of not less than half a pint.

Nicotinic Acid.—The mean daily consumption of this vitamin was also considerably below the recommended dose of 10 to 20 mg., and all the patients with the exception of one received well below this amount.

Observations by Spies and Collins (18) in 1946 seem to indicate a dependency between the B vitamins and the aging processes. Thus the signs considered characteristic of premature senility—aged appearance, lack of initiative, psychologic changes, and reduced activity—are frequent findings in middle-aged patients suffering from malnutrition and especially B-hypovitaminosis. Many old patients who because of an assumed senile dementia had been a burden on the younger members of the family improved so much after treatment with B vitamin and an adequate diet that they were able to be of assistance in the home.

The signs of glossitis and perlèche which were present in all the patients in this study are presumably caused by a degeneration of the epithelial cells which most likely is not confined to the epithelium of the tongue and the lips. By interference with the cellular oxidation processes the vitamin B deficiency probably also affects several other tissues of the body, thus causing degenerative symptoms which may be interpreted erroneously by the clinician as aging processes not amenable to therapy. The findings by Spies and Collins (18) should encourage an active therapeutic attitude towards presumed "degenerative signs of aging."

Vitamin C.—For this vitamin alone was the ingestion sufficient in a number of the patients. The mean intake was 22 mg. for the women and 32 mg. for the men.

Westergaard (21) in 1940 in an investigation of nurses and old patients in De Gamles By found an average serum ascorbic acid content of 0.28 mg. per cent for the nurses, whereas nearly all of the patients showed values of 0.00 mg. per cent in spite of the fact that both the employees and the patients received food identically prepared in the same kitchen.

Studies on the saturation dose for vitamin C performed by Rafsky and Newman (16) and by Fastre and Geubel (7) further show that the dose necessary for saturation is higher in a large percentage of older individuals. A similar elevation of the saturation dose in old age among subjects receiving a vitamin C rich diet was found in 14 patients studied by Gander and Niedberger (8).

It therefore seems to be established that with advancing years there exists a tendency for ascorbic acid deficiency, whether this tendency is conditioned by a decreased intake or a reduced absorption.

Vitamin D.—The knowledge concerning the requirements for this vitamin in old age is very scarce. If a dose of 250 units per day may be considered as adequate for middle-aged persons, the intake of vitamin D by the patients in the present study was greatly insufficient.

In the study of a patient with osteomalacia, Adams (1) made the observation that a greater calcium retention was obtained by administration of tribasic calcium phosphate together with vitamin D than when the calcium phosphate was given alone. It may therefore be assumed that the low vitamin D intake of our patients may have contributed to the development of osteomalacia on the calcium deficient diet.

Discussion

The diet of old institutionalized persons, who due to circumstances frequently are forced to spend their last years or even decades in a hospital, is a subject of considerable importance. While the difficulties of purchasing and preparing the food are eliminated for such patients, the present study shows that nevertheless dietary problems occur. Thus a number of the patients although offered a diet adequate for adult individuals nevertheless had an insufficient food consumption, both with regard to total calories and specific nutrients.

If the requirements for protective foods were lower in old patients than in younger adults,

the observed low food intake might be less significant. It is, however considered not to be the case, as our patients presented signs of deficiency diseases such as glossitis, cheilitis, perlèche, and hypochromic anemia, and previous investigations show that the requirements for protein and calcium in old age are as high or even higher than for middle-aged persons.

The therapeutic conclusions from the present study must be that in a geriatric service attention should be paid to the presence of deficiency diseases in long term hospitalized patients and that the diets of such patients should

TABLE 1. CLINICAL AND LABORATORY DATA ON THE 20 PATIENTS INCLUDED IN THIS STUDY

Women	Age	Weight (Kg.)		Month of Investigation	Comment	Hemoglobin Per Cent	Erythrocytes Millions per Cubic Mm.	Color Index	Daily Milk Consumption in Cups	Diagnosis
		Before Investigation	3 Months after Investigation							
M. J.	85	53.5	50.1	Nov.	Bed	82	4.08	0.95	½-1	Cerebral Arteriosclerosis
A. M. J.	70	57.5		Dec.	Bed	94	4.31	1.04	1	Spastic Hemiparesis
A. E.	80	55.0		May	Bed	68	3.08	1.17	0	Senile Dementia
J. M.	67	52.5	51.0	Aug.	Wheel Chair	66	3.65	0.85	0	Senile Dementia
A. T.	66	52.5		July	Bed	88	4.02	1.06	0	Senile Dementia
K. K. J.	72	52.0		Jan.	Bed	76	3.22	1.11	1	Parkinsonism
V. K.	73			April	Bed	70	3.29	1.01	2	Spastic Hemiparesis
D. S.	82	72.0		July	Wheel Chair	80	3.51	1.14	1	Angina Pectoris
V. H.	72	63.0		Sept.	Bed	85	3.98	1.01	0	Chronic Diarrhea
S. J.	85	53.5	47.5	Aug.	Wheel Chair	87	3.67	1.13	0	Fracture of Hip
A. C.	76	47.5		Dec.	Wheel Chair	82	3.98	0.97	0	Myocardial Degeneration
M. N.	74	78.5	78.5	May	Bed	75	3.48	1.02	0	Myocardial Degeneration
D. J.	81	54.5	53.0	Oct.	Bed	86	2.97	1.35	0	Myocardial Degeneration
E. N.	77	69.5	68.5	Dec.	Wheel Chair	86	3.62	1.13	0	Spastic Hemiparesis
K. M. M.	76	65.0	66.0	Nov.	Wheel Chair	80	2.91	1.31	1	Arthritis of Knees
K. S.	83	75.5	75.0	July	Wheel Chair	80	4.09	0.72	0	Myocardial Degeneration
Men										
V. A.	75	49.5	50.0	Aug.	Bed	85	3.37	1.19	0	Spastic Hemiparesis
M. J.	69	65.0		Jan.	Wheel Chair	80	4.40	0.95	0	Spastic Hemiparesis
A. J.	88	57.5	52.2	Sept.	Bed	77	3.83	0.90	0	Myocardial Degeneration
J. L.	76	63.5	63.5	Oct.	Bed	70	2.77	1.23	½	Myocardial Degeneration

TABLE 2. DAILY CONSUMPTION OF VARIOUS FOOD CONSTITUENTS BY THE 20 PATIENTS

Women	Calories	Protein gm.	Calcium Mg.	Phosphorus Mg.	Iron Mg.	Vitamin A I. U.	Thiamine Micrograms	Riboflavin Micrograms	Nicotinic Acid Mg.	Vitamin C Mg.	Vitamin D I. U.
M. J.	635	20	361	444	3.6	1162	341	681	2.9	10	15
A. M. J.	740	24	378	496	3.2	777	414	693	2.9	30	18
A. E.	872	21	294	442	3.9	1195	353	474	3.0	14	30
J. M.	890	23	192	457	4.5	1345	382	506	5.6	30	92
A. T.	907	26	200	466	3.9	1091	405	584	5.0	42	114
K. K. J.	917	30	442	609	4.2	853	515	746	5.0	15	24
V. K.	972	35	654	812	4.2	1784	516	1114	3.9	18	35
D. S.	1020	24	390	529	3.7	1903	463	757	2.3	38	38
V. H.	1089	34	355	683	5.1	921	467	663	7.5	36	199
S. J.	1091	32	227	509	4.2	1040	442	611	6.1	34	135
A. C.	1178	29	279	552	5.1	1447	483	578	6.0	29	67
M. N.	1221	38	316	651	5.2	2015	592	682	6.6	13	82
D. J.	1225	29	218	459	4.2	1353	562	508	4.9	17	36
E. N.	1240	33	256	632	5.8	1703	526	520	6.8	19	90
K. M. M.	1244	36	560	810	5.7	1881	626	933	6.4	41	34
K. S.	1250	43	321	621	5.4	1853	427	756	7.0	54	44
Average	1037	29	340	573	4.5	1395	470	675	5.1	28	66
Men											
V. A.	1304	37	253	573	4.8	1460	513	706	5.8	46	83
M. J.	1307	37	448	745	6.0	2356	632	753	8.1	21	40
A. J.	1341	43	325	864	9.2	2784	817	874	11.0	33	25
J. L.	1376	36	456	719	5.6	1609	590	677	7.1	26	31
Average	1332	38	371	725	6.4	2052	638	753	8.0	32	45

be supplemented with specific nutrients in order to prevent the last years of these debilitated persons being more miserable.

SUMMARY

Measurements of the actual food consumption of a group of patients in a gerontologic division revealed a total caloric intake and a consumption of proteins, minerals, and vitamins far below the usually accepted standards. Since the food requirement of older individuals is hardly much lower than that of younger adults the nutrition of elderly hospitalized patients should be carefully considered. The importance of supplying an adequate milk intake is emphasized.

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Adaptation in the Phantom Limb Phenomenon as Influenced by the Age of the Amputees

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STUDYING A GROUP OF 173 ARM AMPUTEES, AGED 17 TO 45 YEARS, DR. JALAVISTO OBSERVED THAT THE OLDER SUBJECTS ADAPTED THEMSELVES MORE SLOWLY THAN THE YOUNGER ONES.

THE phantom phenomenon is of interest both to physicians and to psychologists. Papers dealing with it are numerous and have recently been reviewed by Lunn (4) and by Jalavisto and Sourander (2).

A phantom sensation is evoked by peripheral irritation; the cortical area activated by the impulses determines which part of the limb will be present in the phantom. To a certain limit this explanation may be extended to the motor phenomena, i. e., the spontaneous movements of the phantom.

If an amputee is asked to place or move his stump near some object, the wall for instance, so that the phantom would, if perceived in the usual position, enter the wall, the patient is frequently greatly surprised because the phantom sensation either fades away, the phantom hand is suddenly perceived within the stump, or the phantom arm shrinks away from the wall. These alterations of the phantom sensation occur, however, only in part of the subjects. In other amputees the phantom hand is perceived as before outside the stump and consequently within the wall. These observations were already described in 1920 by Katz (3), but to my knowledge no attempt has ever been made to find out the conditions responsible for the difference in reaction in various amputees.

In a recent paper Henderson and Smyth (1) observed this phenomenon of what I called "obstacle shunning" and claimed to have found it only when the stump came into contact with the wall. In the present cases, however, contact of the stump with the wall was carefully avoided.

The present paper deals with the effect of age on the phantom sensation.

Material and Methods

The material consists of 173 arm amputees between 17 and 45 years of age from the Finnish wars of 1939-1940 and 1941-1944. The age distribution of the patients is given in table 1. Most of the examinations were made only once on each patient. The time between the amputation and the test varied from twenty-one days to three years and nine months; the majority of the subjects were examined eight to ten months after the amputation. The few cases on which a reexamination took place were treated as separate cases.

The material is equally divided between right and left upper and forearm amputations. About 25 per cent belongs to each of these groups.

In the performance of the tests the patient was asked to give a detailed account of the character of the phantom sensation and to describe the sensation when he was placed near a wall or table and had to move the stump so that the phantom, if unchanged, would occupy some place within the wall or the table (obstacle shunning experiment).

Special attention was given to the following points: 1) was the phantom still perceived, 2) was it perceived as being outside the stump or within it, and 3) when the stump was held near some obstacle, a) did the phantom sensation disappear, b) did it shun the obstacle, or c) did it become located within the stump?

The patients were divided into groups according to the presence of the phantom sensation and the reaction in the obstacle shunning experiment. A grouping was further made on the basis of the age of the patients (under 25

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years, 25 to 29 years, 30 to 45 years) and on the time elapsed between amputation and examination (within six months, after six months). The distribution of the cases was statistically evaluated by means of the Chi-square test.

Results

The classification of the patients according to the phantom sensation is given in table 2 in which the first three groups are considered as representing an adaptive reaction, whereas the two last groups constitute a fixed rigid reaction. In every patient the phantom-like sensation had been present for some time after the amputation. Since the investigation usually was carried out within one year after the amputation the number of cases in which the phantom had disappeared was small.

If the age distribution for the 5 perceptive groups in table 2 is examined a difference will be noted (see table 3). Thus both in groups 1, 2, and 3 the younger age group (17 to 24 years) is twice or three times as numerous as the older age groups. The difference is already notable between this group and the group of men 25 to 29 years old. No such difference appears in groups 4 and 5, but the number of cases is so small that the significance of the difference is uncertain and the Chi-square test cannot be applied. If groups 1 to 3 and groups 4 and 5 are treated as two different categories and the age groups younger than 25 and older than 25 as two further groups, tables 3 and 4 distinctly show the difference in distribution and the statistical significance can be verified by the Chi-square test ($P = 0.35$ per cent).

In the foregoing computation no distinction has been made between those patients who had been examined within less than six months after amputation and those for whom a longer time had elapsed since the amputation. In table 5 the age distribution within the perceptual groups arranged according to the time of examination is given. The table shows that in the examinations performed after six months a larger number of cases are classified as belonging to groups 1 to 3; this is especially noticeable as far as the older patients are concerned.

The age difference is therefore more apparent in the examinations performed within six months after the amputation than after this period. This is not surprising, since if the perceptual behavior of groups 1 to 3 is dependent on adaptive processes, it is natural that these should manifest themselves earlier in the young patients. If the older patients are given more time they may reach the same degree of adaptation as the young subjects. Consequently the relative number of amputees belonging to groups 1 to 3 must increase in the older age groups with a lengthened interval after the amputation.

Discussion

The question of whether it is justifiable to classify groups 1 to 3 together deserves some consideration. Are the disappearance of the phantom, the perception of the phantom as being within the stump, and the obstacle shunning adaptation phenomena and as such comparable? The concept of adaptation implies some agent or stimulus which requires adaptation and the process of adaptation, which tends to abolish the effect of the stimulus.

In the phantom phenomenon both the stimulus and the process of adaptation are most probably represented by psychic events rather

than by peripheral nervous mechanisms. The conflict of the actual sensation of a (three dimensional) phantom limb, with the experience of objects sometimes occupying the same position in space as the phantom, without, however, eliciting any sensation of contact, is felt by most amputees to be very unpleasant. It may therefore be regarded as a distressing stimulus requiring adaptation.

TABLE 1. AGE DISTRIBUTION OF THE MATERIAL

Years	Number
17–20	11
20–24	65
25–29	51
30–34	31
35–45	15
	173

TABLE 2. CLASSIFICATION OF PATIENTS ACCORDING TO THE PHANTOM SENSATION

Perceptual Group	Phantom at Examination	Patients	
		Number	Percentage
1	Not present	24	14.0
2	Located within the stump	25	14.5
3	Disappears or "shuns" the obstacle when the stump is placed near the wall	35	20.0
4	Occupies a place within the wall	62	36.0
5	Statements vague	27	15.5
	Total	173	100.0

It can easily be seen that there are only three possible modifications of the phantom sensation capable of preventing this conceptual conflict between phantom sensation and physical objects, the disappearance of the phantom, the location of the phantom within the stump, or the adoption of the behavior called obstacle shunning.

Each of these alterations of the phantom sensation forms a perfect solution of the conflict situation and may thus be considered as an equally good adaptation. In this sense groups 1 to 3 belong together. In this connection, however, it may be argued that the persistence of the phantom phenomenon is entirely dependent upon the presence of irritation of the stump, or in other words, if the healing proceeds without disturbances the phantom sensation fades away.

A study of the case histories of the patients revealed that absence of pain actually occurred more frequently in the younger age group (see table 6), but that the difference between the younger and older age groups as far as this symptom was concerned was not statistically

TABLE 4. AGE GROUPS CLASSIFIED ACCORDING TO PERCENTAGE OF ADAPTABLE AND RIGID SUBJECTS

Age Group	Percentage of Subjects	
	Adaptable	Fixed, Rigid
17–24	62	38
25–29	37	63
30–45	39	61

TABLE 3. AGE DISTRIBUTION OF THE FIVE PERCEPTUAL GROUPS

Age Group	Adaptable Group (Sub-Groups 1, 2, and 3)				Fixed, Rigid Group (Sub-Groups 4 and 5)			Sum Total
	1	2	3	Total	4	5	Total	
Under 25	15	13	19	47	22	7	29	76
25–29	3	6	10	19	23	9	32	97
Over 30	6	6	6	18	17	11	28	
	24	25	35	84	62	27	89	173

$\chi^2 = 9.39$ P = 0.35% (See Text)

TABLE 5. AGE DISTRIBUTION WITHIN THE PERCEPTUAL GROUPS ACCORDING TO TIME OF EXAMINATIONS

Age Group	Examinations Less Than 6 Months After Amputation			Examinations More Than 6 Months After Amputation		
	Group 1–3 Adaptable	Group 4–5 Fixed	Total	Group 1–3 Adaptable	Group 4–5 Fixed	Total
Under 25	24	17	41	30	19	49
Over 25	8	24	32	35	46	81
	32	41	73	65	65	130
	$\chi^2 = 8.14$ P = 0.5%			$\chi^2 = 4.0$ P = 4.5%		

significant (probability above 5 per cent). It is nevertheless possible that the greater healing tendency in the young subjects furthers the disappearance of the phantom sensation, but it cannot be the sole cause. It is not likely, however, that the absence of pain can explain the difference in the age distribution of the amputees belonging to group 2 and particularly to group 3 where the phantom sensation is modified by an external although purely conceptual change which is unrelated to the condition of the stump; and these latter groups form the main part of groups 1 to 3.

TABLE 6. DISTRIBUTION OF PAIN IN THE MATERIAL

Age Group	Pain Absent		Pain Present		Total
	Number	Percentage	Number	Percentage	
17–24	30	39.5	46	60.5	76
25–45	25	25.8	72	74.2	97
	55	31.8	118	68.2	173

$\chi^2 = 3.79$ P = 5.1%

SUMMARY

An analysis was made of 173 arm amputees of the adaptability of the phantom sensation in relation to the age of the patients. The processes considered as adaptation were: disappearance of the phantom sensation, location of the phantom within the stump, and obstacle shunning of the phantom when the stump was moved near a wall.

It was found that these adaptation phenomena developed earlier after amputation and were more frequent (62 per cent) in the young amputees (17 to 24 years old) than in the group of older patients (38 per cent, 25 to 45 years old).

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Connective Tissue Fine Structure and Some Methods for Its Analysis

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IN THIS SURVEY DR. GROSS REVIEWS THE PROCEDURES FOR INVESTIGATION OF THE SUBMICROSCOPIC STRUCTURE OF CONNECTIVE TISSUE AND GIVES AN OUTLINE OF THE PRESENT STATE OF KNOWLEDGE IN THIS IMPORTANT FIELD. PRELIMINARY DATA ON COLLAGEN AND ELASTIN STUDIES OF AGING TISSUES ARE ALSO PRESENTED.

FINE structure or ultrastructure analysis is that discipline which deals with the molecular and colloidal organization of biologic materials (46, 113, 115, 116, 120). Although the techniques involved often require examination of isolated and purified systems, the overall goal is to obtain information concerning the structure and reactivity of these systems and to relate them to the dynamic state of the parent tissues. To succeed in this ambition requires the application of as many relevant tools of the biologist, physicist, and chemist as is possible. Any single method has severe limitations and requires supplementation from other directions.

The importance of structural organization on a molecular and colloidal level is evident. Phenomena such as muscular contraction, intracellular sol-gel transformations, antigen-antibody reactions, hormone and enzyme activity, and membrane permeability are highly dependent on molecular structural configuration and colloidal interaction.

Qualitative and quantitative studies of the simple building blocks of a macromolecule, viz., the amino acids in a protein, yield but little information concerning the reactivity and specificity of the parent substance. Yet in combination with a knowledge of the structural and dynamic properties of the macromolecule much can be learned of its biologic activity. The same argument holds for the relationship of the large molecule to the tissue. In general, the properties of a purified tissue component only give leads to the properties of its parent complex. However, it is essential to study in detail the characteristics of well-defined and purified tissue components in order to disentangle the complex interrelated properties and reactivity of the tissue.

The dimensional range of fine structure analysis extends from a few Angstrom units to about 0.2 μ—from the size of the simplest organic molecules to structures just visible in the light microscope. There is a large armamentarium of physical-chemical and biophysical techniques from which one may select those tools most valuable for the dimensional range and type of information desired.

Physical-chemical methods such as ultracentrifugation, electrophoresis, viscosity, streaming birefringence, diffusion, osmotic pressure, and dielectric constant measurements provide much valuable information concerning the homogeneity, size, shape, weight, and electrical properties of large molecules and particles (28, 37, 38, 76, 128, 131). However, these methods up to the present are limited chiefly to the investigation of purified components in solution. Certain important types of colloidal particles such as the long fibrous macromolecules composing the fibrils of collagen are extremely difficult to study with these tools because of the high degree of molecular interaction in solution which interferes with interpretations relating to the individual particles.

Studies of the thermodynamic properties of biologic materials such as thermoelastic behavior and force-extension relationships so useful in the study of high polymer system (1) can provide valuable information concerning the mechanical properties of tissues (68, 79, 80). However, they should be used with ex-

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treme caution in deducing fine structure. This type of study describes the over-all reactivity of the tissue and provides no information concerning the nature of components which do not contribute to the particular properties being measured.

Ultraviolet (30, 86, 123), infra-red (19, 69, 7), and roentgen ray (41, 42, 43, 48) microspectroscopy are extremely valuable for the localization of certain substances and types of chemical bonds in cells and tissues; however, they are limited by relatively low resolving power and are therefore of little value at present in the study of structure in the colloidal range.

Continued progress in morphologic investigations, so rapid during the nineteenth century with the aid of the microscope, was inevitably slowed as a result of the ultimate limitation in resolving power of light microscopy. This limitation imposed by the long wavelength of visible light (resolving power being an inverse function of wavelength and directly proportional to numerical aperture) was evaded in special ways by dark-field and polarized light microscopy. Particles as small as 500 A and less in one or more dimensions could be detected by reflected light in the dark field. The best resolution obtained by the light microscope is about 2000 A or 0.2 μ. Ultraviolet illumination improves this figure by a factor of about 2 (123). The polarizing microscope permits the detection of oriented asymmetric particles of "submicroscopic" dimensions.

With the advent of roentgen rays and electrons great increases in resolution became possible and the domain of morphology was extended to include colloids, molecules, and even atoms. The extremely short wavelengths of roentgen rays and electrons (determined by the accelerating voltage) makes possible the increase in resolving power.

Roentgen Ray Diffraction.—The resolving power obtainable by roentgen ray diffraction methods at the present time exceeds that of the electron microscope because of the much larger aperture with roentgen rays. The diffraction patterns obtained at wide apertures (using copper Kα radiation), known as wide angle patterns, are produced by diffracting units of the order of size of atoms and small molecules, ca. 20 A and less. Patterns taken at small apertures result from larger diffracting units such as macromolecules and structures of colloidal dimensions roughly of the order of 100 to 1000 Å (20). Thus, small angle diffractions overlap the most effective dimensional range of the electron microscope.

Unfortunately, roentgen rays are not readily focussed to give direct images; hence it is necessary to rely upon mathematical interpretations of diffraction patterns produced by orderly arrays of atoms and molecules. Because sharp, diffraction-rich patterns are not produced by disordered systems this otherwise invaluable technique is disappointing when applied to amorphous substances. However, diffuse small angle roentgen ray scattering has been used to determine average particle size in colloidal systems (44, 109).

Well oriented specimens of known composition are highly desirable for roentgen ray studies. However, a complex tissue is amenable to study if the diffraction patterns of all its components are known. Orientation of the diffracting elements by some procedure such as stretching is also desirable. Specimens can be quite thick (ca. 1 mm.) and can be examined in the wet state.

Obtaining the diffraction pattern is the simplest part of the procedure; interpretation provides the greatest hurdle. It is usually necessary to combine information derived from other sources with diffraction theory to reconstruct the diffracting system. One of the very profitable procedures is to devise various hypothetic models, selecting the one which best fulfills the conditions required by the data. Both these procedures have been used by Bear and Bolduan (11) in arriving at a detailed description of collagen structure, to be discussed later.

One of the recent triumphs of this technique has been the elucidation of the structure of penicillin which led to its synthesis—a feat analytic chemistry alone failed to accomplish (34). In addition to its application to fine structure problems, roentgen ray diffraction can be used in microqualitative analysis. Gross and Oberst (56) have identified at least 14 opiates of the morphine group in 0.7 μg. quantities by their unique diffraction patterns.

Polarized Light.—Polarization optical methods are among the oldest procedures used in fine structure studies. Valentin in 1861 investigated the structure of nerve and many other tissues with polarized light.

Fresh, living tissues can be examined with the polarizing microscope and information may be obtained concerning the presence and direction of orientation of fibrous or platelet type particles with one dimension smaller than the wavelength of the incident radiation. In addition, information concerning crystallinity, partial volume, and refractive index of birefringent particles is also obtainable (13, 112, 121).

Polarized ultraviolet (dichroism) studies permit deductions concerning orientations of certain ultraviolet absorbing constituents of oriented macromolecules (30). Polarized infra-red microscopy, a recent development, may provide data on orientations of certain chemical bonds in highly ordered substances (19).

Electron Microscopy.—Of all direct imaging optical instruments the electron microscope has the greatest resolving power, the theoretic lower limit lying between 1 and 10 Å, less than the width of the average polypeptide chain. In practice, however, because of lens aberrations and lack of specimen contrast, 20 A is about the best resolution for biologic materials one may expect at present. The optical principles of the electron microscope are essentially the same as those of the light microscope. The illuminating radiation is a high velocity, monochromatic beam of electrons, which are focussed by magnetic or electrostatic lenses. Because electrons are scattered by air, it is necessary to establish a high vacuum along the path of the beam. The specimen is readily manipulated on a mechanical stage and the image viewed on a fluorescent screen for selection of fields for photographing. Viewing magnifications with the RCA instrument ranging from 800 to 20,000 X are obtained by simply setting a dial. Subsequent enlargements of high resolution micrographs to more than 200,000 X are feasible (29, 39, 47, 62, 74, 75, 120, 141, 133).

There are certain strict requirements for the preparation of a satisfactory specimen: the material must be completely desiccated because it is examined in a high vacuum; it must be of the order of 0.01 to 0.5 μ thick in order to permit penetration of the electron beam and resolution of fine details. One important requirement for good electron microscopy is adequate statistical sampling of specimens because of the fantastically small amount of material examined on a single specimen—measured in hundredths of a microgram. The need for some statistical uniformity of a large number of *identifiable* objects obtained from different portions of the material being studied is obvious. Since such particles bear no labels, it is necessary in the study of a complex tissue to have previously established the "fingerprint" (and its normal variations) of all the components present. This usually requires a study of the purified component or of tissue consisting mainly of that constituent.

The effect of the electron beam on the specimen can be serious if one is not judicious in controlling the intensity of illumination. How-

ever, such artifacts, if they occur, are generally easy to recognize with some experience. A more serious artifact is the effect of surface tension in drying which can produce considerable distortion. This effect is most difficult to evaluate in the study of unstable materials such as protoplasm and quite simple in the case of the fibrous structures of the connective tissue. Occasionally drying patterns can help furnish information concerning the properties of the material as in the case of hyaluronic acid (51), rubber (60), and other polymers. The well-known difficulties in evaluating the effects of fixatives in ordinary histology are multiplied greatly in electron microscopy of fixed material. However, a study of the colloidal effects of various fixatives could provide much valuable information concerning their mode of action. Such studies are under way in the Biology Department at Massachusetts Institute of Technology and elsewhere. The distortions caused by optical aberrations, poor focussing, and specimen movement produce serious errors in interpretation and should be corrected as far as possible.

Most used methods of specimen preparation include fragmentation by teasing, blending, homogenizing, sonic disruption, thin sectioning, surface replication, and the culturing of cells on the plastic specimen screen. Metal shadowing and "electron staining" are invaluable adjuvant techniques.

Sectioning methods have been improving rapidly with the modification of the ordinary histologic microtome so that it can cut serial sections thinner than 0.1 μ (99). Recent improvements include plastic imbedding procedures (95) and the substitution of fractured glass for the steel knife (83).

Methods of producing faithful replicas in plastic films and silica have made it possible to examine surfaces of electron opaque specimens, to study dry (8, 52, 108, 111) and moist material (40, 52, 73), and also actually to visualize the individual molecules in crystallized proteins such as edestin (64, 65) and catalase (66).

The technique of tissue culture devised by Porter and associates (36, 103, 104, 105) permits cells to grow out exceedingly thin on a coverslip, coated with the plastic supporting film, which is then removed and placed on the wire mesh grid for examination. Intracellular fine structure, host-virus relationships, (140) and the production of extracellular connective tissue (107) are being fruitfully studied in this manner.

Significant contributions of electron microscopy may be expected from the study of dynamic processes such as fiber formation, as in the case of the fibrinogen-fibrin transformation (63, 70, 106), and globule—fibril reversibility as described for insulin (130), actin (77), and tropomyosin (4, 5). A study of the physico-chemical conditions required for the formation of the regularly repeating axial fine structure of collagen fibrils in progress in this Department (122) is expected to throw light on the nature of the bonding between the polypeptide chains. Electron microscopy can have much application in evaluating morphologic homogeneity in tissue extracts as well as providing a direct visual check on the sizes and shapes and weights of macromolecules as determined by indirect physical-chemical methods.

The procedure of metal shadowing devised by Williams and Wyckoff (132, 134) involves the deposition of a film of suitable metal a few Angstrom units thick on to the surface of the material, previously dried on the supporting film of the specimen grid, by evaporation in a vacuum chamber. With the surface of the specimen placed at a small angle to the "point" source of evaporating metal there is a piling up of the metal on the near side of the object and an absence of metal in the "lee" of the object, thus producing a shadow whose length is a simple trigonometric function of the height of the object and the angle between specimen film surface and the normal to the evaporation source. This produces a great increase in image contrast, a three dimensional effect, and permits visualization of extremely small particles otherwise invisible.

Staining of material for electron microscopy has barely begun but will probably prove to

be a most fruitful procedure. It requires the deposition on, or combination of, a compound containing a heavy atom with the object in order to produce a sharp, local increase in electron scattering. To date considerable detail has been revealed in the structure of collagen (52, 117, 118), fibrin (63), and paramyosin (61) by the use of phosphotungstic acid staining. However, real progress will lie in the application of "electron stains" which are highly specific for certain chemical groups. Phosphotungstic, phosphomolybdic, and osmic acid, chiefly the heteropoly acids, now in use are far from specific. When cytochemical methods for localization of enzymes and other substances are refined so as to be truly specific and localizing they should prove to be of immense value in electron microscopy.

Collagen.—The connective tissue, collagen in particular, has received intensive study from the point of view of analytic and physical chemistry, mechanical properties, and fine structure. The amino acid analysis of some forms of collagen is thought to be practically complete (22, 23, 24, 31, 49, 78, 94). Its amino acid pattern differs from that of any other protein in several ways: there is an almost complete absence of aromatic amino acids (85) and an unusually high content of proline, hydroxyproline, and hydroxylysine. There is little or no sulfur present. The presence of a small amount of firmly bound carbohydrate has been reported (12). About 38 per cent of the amino acid residues are polar with a very nearly equal number of free basic and acidic groups. The isoelectric point of native beef tendon or hide collagen is about pH 7.0 (57).

There is no good evidence that native collagen is attacked by trypsin (124) although it is rapidly digested by pepsin at low pH (125).

Collagen is highly heat sensitive. At 40 to 60 C wet collagen shrinks suddenly and extensively and with further increase in temperature it dissolves to form gelatin. The critical shrinkage temperatures depend upon the type of tissue and the presence of salts, acids, alkalis, detergents, hydrating, dehydrating, and tanning agents. Careful studies of the swelling, shrinkage, and solution of collagen have produced much valuable data concerning the nature of its inter- and intramolecular structure (25, 26, 27, 57, 84, 93). It should be stressed that there are significant differences in amino acid content and physical-chemical reactivity of collagens from different sources (see table 1). For example, the collagen of the fish swim bladder, known as ichthyocol, is reported to contain about a third the amount of glycine and hydroxyproline and nearly twice as much alanine, serine, and threonine as does mammalian hide collagen (14). Ichthyocol shrinks at a much lower temperature and dissolves in dilute acids whereas hide collagen only swells. A careful study of the properties of collagen from different tissues may well be most rewarding.

Immunologic studies of purified collagen have thus far failed to reveal any appreciable antigenicity (129).

Early histologic studies indicated the fibrous nature of collagen and suggested the existence of a hierarchy of fibrous sizes, namely the macroscopic fiber bundle, composed of microscopic fibers which in turn are made up of fibrils detectable by the dark field microscope (82). Polarized light studies of collagen fibers reveals both positive form and intrinsic birefringence which indicate that the molecules are fibrous and are oriented parallel to each other (82, 101). This information is confirmed by electron microscope and roentgen ray diffraction evidence. It does not support the conclusions of Wyckoff (141), who has recently claimed that collagen fibrils are made up of a series of discs or rings.

The most significant advances in our knowledge of collagen structure has resulted from the combination of roentgen ray diffraction and electron microscope data.

Roentgen ray diffraction studies of fibrous proteins took a large step forward with Astbury's classification of two major groups of protein fibers based on two distinctive wide angle diffraction patterns (2, 3). The "KMEF" class includes keratin, myosin, epi-

dermin, and fibrin, and all other fibrous proteins giving the same wide angle pattern. The second category is designated the collagen class. This includes all forms of white fibrous connective tissue of the vertebrates, ichthyocol from the fish swim bladder, elastoidin of fish scales and fins, "ovokeratin" of the skate egg capsule, "ascarocollagen" from the cuticle of the worm, ascaris, certain fibers of coelenterates and echinoderms and "spongin" from the fibrous skeleton of sea sponges (3, 87). The reticulin of newborn rat skin as defined by its argyrophilia has been shown by Gross and Bear (unpublished) to exhibit the characteristic wide angle pattern of the collagen class. The well-defined collagen wide angle pattern is characterized by two diffuse equatorial spots one at about 11 to 15 A, the second still more diffuse arc at about 5 A, and a short meridional arc at 2.85 A. If the preparation is well oriented, a meridional layer line is evident at about 9.8 A (2, 10).

The innermost equatorial spot supposedly represents the side chain spacings between parallel polypeptide chains, and the outer equatorial arc is supposed to represent the backbone spacing. The side chain spacing is increased somewhat with hydration. The meridional arc is said by Astbury to reflect the average amino acid length and is smaller than that for other proteins (3.4 Å) because of the kinking produced by the high proline and hydroxyproline content. However, Marks, Bear, and Blake (87) have shown the same 2.86 Å spacing for spongin which has little of these two amino acids. A recent comparative study by Marks, Bear, and Blake (87) of the small angle roentgen ray patterns of the fibrous proteins of certain of the various phyla mentioned above has further demonstrated the intimate structural relationship between these substances and vertebrate collagen. It is important to note that although there are sharp qualitative and quantitative differences in the amino acid content of the various members of the collagen class, there is great similarity in their molecular organization. Astbury and Marks, Bear, and Blake (87) have emphasized the importance of such studies from the standpoint of comparative biomolecular structure. The comparative approach may provide much valuable information on the architecture of structural proteins by permitting a study of simpler progenitors of the better known but more complex vertebrate forms.

The early small-angle studies of tendon by Bear, (9, 10) and Kratky and Sekora (81) gave evidence of a highly precise repeating unit along the fiber axis of about 640 A in the dry material and 670 to 690 Å in the wet preparation. Nearly simultaneous electron microscope studies by Hall, Schmitt, and Jakus (59, 114) and Wolpers (135) visually demonstrated this periodicity in dried collagen fibrils from many sources, including tendon. Variation in the intensity of the different orders of the diffraction pattern indicated structural inhomogeneity within the axial repeating period and again electron microscopy confirmed and localized these variations.

Recent studies by Bear and Bolduan (11, 21) on wet and dried kangaroo tendon have resulted in their postulation of the following model. The fibril is composed of a parallel array of polypeptide chains, each roughly 10 Å in diameter. The chains of undetermined length consist of amino acids arranged in a highly specific, yet unknown, order. When these molecules are aligned parallel their like regions fall into register and are bonded to each other laterally. The axial repeating units giving rise to the diffraction patterns and the cross striations observed in the electron microscope arise from repeating regions of imperfect matching, laterally and axially, alternating with regions of crystalline perfection. This alternation of perfect and imperfect regions is evident in dried preparations only. When the tendon is saturated with water, evidence of imperfection in lateral matching is abolished and, as one would expect, there is a slight increase in the long spacing. This structural picture does not preclude the possible presence of more than one molecular species.

Collagen has proved to be an ideal material for study with the electron microscope because

its highly structured units, the fibrils, are of colloidal size in two dimensions, have a distinctive label in the form of a regular axial repeating period averaging 640 Å and intraperiod fine structure, are relatively resistant to mechanical manipulation, and are readily obtainable.

If a bit of collagenous tissue is fragmented by teasing with needles, blending, and homogenizing, a suspension of fibrils is obtained which is then allowed to sediment from a drop onto the supporting collodion film of the specimen grid and air dried. Usually such a crude preparation has in it a considerable amount of amorphous debris representing ground substance, serum proteins, and salts, and requires cleaning by some procedure such as washing in water by centrifugation and in many cases tryptic digestion of noncollagenous material. Figure 1 is an electron micrograph of bundles of collagen fibrils from an aged human skin dispersed by gentle teasing with needles. This arrangement of interlaced bundles is probably characteristic of the intact tissue.

Collagen fibrils extend many microns in length and range from about 200 to roughly 2000 Å in width depending on the tissue. In some tissues fibril widths are quite uniform and in others there is marked variation, as will be discussed later. All forms of vertebrate collagen examined to date are characterized by an axial repeating period of extreme regularity manifested by alternating dark and light bands (114). In rare instances intraperiod banding is observed in unstained, unshadowed preparations.

Staining such a preparation with phosphotungstic acid results in the appearance in most fibrils of 3 to 7 intraperiod striations of characteristic relative density and position within the long spacing (52, 118) (fig. 2). It is believed in this laboratory that the presence of a large number of intraperiod bands represents more exact lateral matching between filaments (118), whereas Wolpers (138, 139) claims that only 3 intraperiod bonds are normally present and splitting of these bonds represents abnormal alteration. There is no evidence yet that phosphotungstic acid (PTA) reacts with specific chemical groups in collagen. It is believed that PTA is either bound nonspecifically to the protein and reflects periodic differences in protein content or fills in spaces in the imperfect regions.

Metal shadowed, nonstained preparations reveal a periodic alternation in thickness along the fibril which corresponds in period and position to the bands observed in PTA stained material. In addition, one may observe in many instances, fine longitudinally arrayed filaments which make up the fibril (118). These probably represent small bundles of polypeptide chains.

Shadowed collodion replicas of moist skin collagen fibrils indicate that the wet fibril is relatively smooth and uniform in diameter along its axis and that the periodic corrugation appears during dehydration (52). This suggests that the alternating periodic regions of the fibril are differently hydrated. This agrees well with the roentgen ray diffraction picture previously described.

A significant difference exists between certain collagens in the strength of intrafibrillar lateral bonding. Fibrils from the fish swim bladder and rat tail tendon exhibit considerable fraying at broken ends and the axial period is carried into each frayed portion of the fibril. Mammalian skin collagen, on the other hand, has very rarely been observed to fray (118). The ends of broken fibrils are either cleanly ruptured, evenly tapered to a point, or surrounded with small amounts of amorphous, disoriented material. This difference is further evidenced by the greater uniformity of fibril width in skin preparations.

Both rat tail tendon and ichthyocol dissolve to produce clear, viscous solutions in dilute acids whereas the greatest proportion of skin collagen only seems to swell in dilute acid, maintaining intact the axial fine structure. Lateral disaggregation of weakly bonded collagen fibrils can be accomplished by various other means, including detergents and strong solvating agents. The relative strength of lateral bonding in collagen from different

tissues has barely been studied and may be of considerable importance in pathology.

Nageotte (92, 93) described a precipitation of fibrils from acid solutions of rat tail tendon by increasing the salt concentration. This has also been observed by Faure-Fremiet (45) for ichthyocol. Schmitt, Hall, and Jakus (114), in repeating this experiment, were able to obtain evidence of periodic cross striations in the precipitated fibrils. Schmitt and Gross (122) in a study of the factors involved in the formation of cross striated fibrils from acid solutions have been able reproducibly to reconstitute collagen fibrils with the same period and fine structure as the fibrils of the starting material.

In view of all the evidence suggesting extracellular synthesis of collagen fibrils it is a reasonable supposition that the cell secretes a precursor, probably the polypeptide chains; alteration of the physical-chemical conditions outside the cell causes these building blocks to associate in a manner similar to that of the Nageotte experiment. Porter and Vanamee (107) have recently described, in a preliminary paper, an electron microscope study of the synthesis of collagen in fibroblast tissue cultures. They observed in addition to typical collagen fibrils small nodular filaments and some larger, finely straited fibrils which they believe to represent stages in the extracellular development of collagen. They suggest that the smallest collagen filaments are composed of chains of globular protein molecules. This type of study shows great promise as a means for investigating the synthesis of structural materials.

A recent study of the aging changes in the collagenous connective tissue of rat skin was undertaken by Gross (55). Histologic, roentgen ray diffraction, and electron microscope studies were carried out on the skins of animals ranging in age from 2 days to 3 months. Silver staining procedures (modified Bielchowsky) indicated that nearly all the fibrous elements of the corium of 2 to 12 day old rats are argyrophilic, hence, by most definitions, are reticulin. With increase in age, there is a continuous decrease in proportion of argyrophilic fibers, suggesting either a transition of so-called reticulin to collagen or an increase in collagen deposition compared to that of reticulin. Electron microscope studies of fragmented corium of all age groups demonstrated the characteristic cross striated fibrils with an average period of 640 to 650 Å.

Fibrils of the newborn animal skin averaged 500 to 600 A in width (fig. 4), the gaussian distribution curve showing very little dispersion. Beyond the age of 12 days there was a steady increase in the average fibril width with a marked broadening of the distribution curve. Average fibril width began to level off at 60 days of age at 1300 to 1500 Å. Fibrils from a 90 day old rat skin are illustrated in figure 3. In a few very rare instances a 500 Å wide fibril was observed to increase in width within a short length to about 1200 Å.

Electron micrographs of Bielchowsky-stained tissues revealed an irregular surface adsorption of metal particles of colloidal size, usually in random fashion. Both the intensely argyrophilic newborn collagen and the purple tinted adult collagen adsorbed metal particles but in the latter instance there seemed to be greater variation in particle size and shape. The study of argyrophilia is still in progress. One striking difference between the mature and immature connective tissue is the highly gelatinous appearance and behavior of the latter. This feature was also observed in human skin (52). Blending or homogenizing reduces the young tissue to small clumps of fibrils embedded in a jelly-like matrix. In order to obtain large numbers of clean fibrils for adequate study with the electron microscope, it was necessary to destroy the amorphous matrix with trypsin (54). The fibrils are not attacked by this enzyme.

Roentgen ray diffraction studies of rat corium of various ages are now being carried on in collaboration with R. S. Bear. Wide-angle diffraction patterns of newborn corium are typical of collagen, in contrast to those described by Heringa and Weidinger (71) which consisted of two diffuse rings not related to the classic collagen pattern. Superimposed on

the wide-angle pattern obtained in our laboratory was a diffuse broad halo which could be eliminated by treating the tissue with trypsin. This was most probably the contribution of the voluminous, amorphous ground substance.

Orekhovitch and associates (97, 127) in a series of papers have described the extraction from various collagenous tissues of a fibrous protein which they have called "procollagen." The extracting media were dilute organic buffers, particularly citrate, in the pH range 3 to 4. The extract is a viscous solution which, when dialyzed against water, produces long needle shaped fibers. Amino acid analysis of this material revealed a collagen-like pattern (32). This extract differs from the Nageotte acetic or formic acid extracts in that the latter only form transparent gels on dialysis against water.

Highberger, Gross, and Schmitt (72) in a recent paper have described the electron microscope appearance of fibrils formed by the Orekhovitch procedure. In addition to the presence of collagen-type fibrils in certain preparations, a fibril having an axial spacing of about 2200 Å obtained from rat skin and steer hide extracts was found. Depending on the pH of the preparation these structures form long fibrils or short, flat single segments. There is a very characteristic intraperiod banding present. It is not yet determined whether these structures represent a modified collagen or a second component of the collagen fibril. An intensive study of this material by electron microscopy, roentgen ray diffraction, analytic chemistry, and physical-chemical methods are in progress. Age, species, and tissue differences are being investigated. The authors believe that at present there is insufficient evidence to support the contention of Orekhovitch that this substance is a precursor of collagen.

Elastic Tissue.—Elastic fibers comprise the second formed element of the connective tissue. Histologically they appear as branched fibers of variable length and width and as fenestrated laminae in blood vessels. These fibers differ from collagen in many ways. They are yellow in the native state, resistant to boiling water and dilute acids and alkalis. Unlike collagen they are susceptible to tryptic digestion. They exhibit a long range elasticity and great mechanical strength. The amino acid distribution of elastin (94, 126) is stated to be quite different from that of collagen in that roughly 1 in 30 amino acids are polar in contrast to about 39 per cent for collagen. The large number of nonpolar residues is probably a major factor contributing to the elasticity of these fibers.

Force-extension and thermoelastic studies of elastic tissue (91) have revealed a mechanical behavior remarkably similar to that of rubber and has led to the widely accepted conception of the molecular organization of this tissue as being a completely disordered, tangled mass of long relatively apolar polypeptide chains, closely analogous to the molecular model for rubber.

Polarized light studies by Schmidt (112) have revealed detectable birefringence in elastic fibers on stretching only. Astbury's roentgen ray diffraction studies of elastin which had been autoclaved to remove the closely associated collagen revealed no evidence of ordered structure (3). Both these investigations established confidence in the rubber-like model. An electron microscope investigation by Wolpers (136) of elastic tissue partially digested with pepsin and fixed with osmic acid revealed long fibrillated but otherwise amorphous fibers in ligamentum nuchae and thin fenestrated laminae in mouse aorta. However, a recent study of elastic tissue structure with the electron microscope by the author has revealed a complex and partially ordered structure for the elastic fiber (53).

Electron micrographs of fragmented elastic tissue from many sources appear as described by Wolpers although laminae were not observed in arterial tissue (fig. 5). If the tissue is not predigested with pepsin, or boiled, collagen fibrils can be seen to pass into the substance of elastic fibers (53), probably having been incorporated incidently during the synthesis of the latter (18).

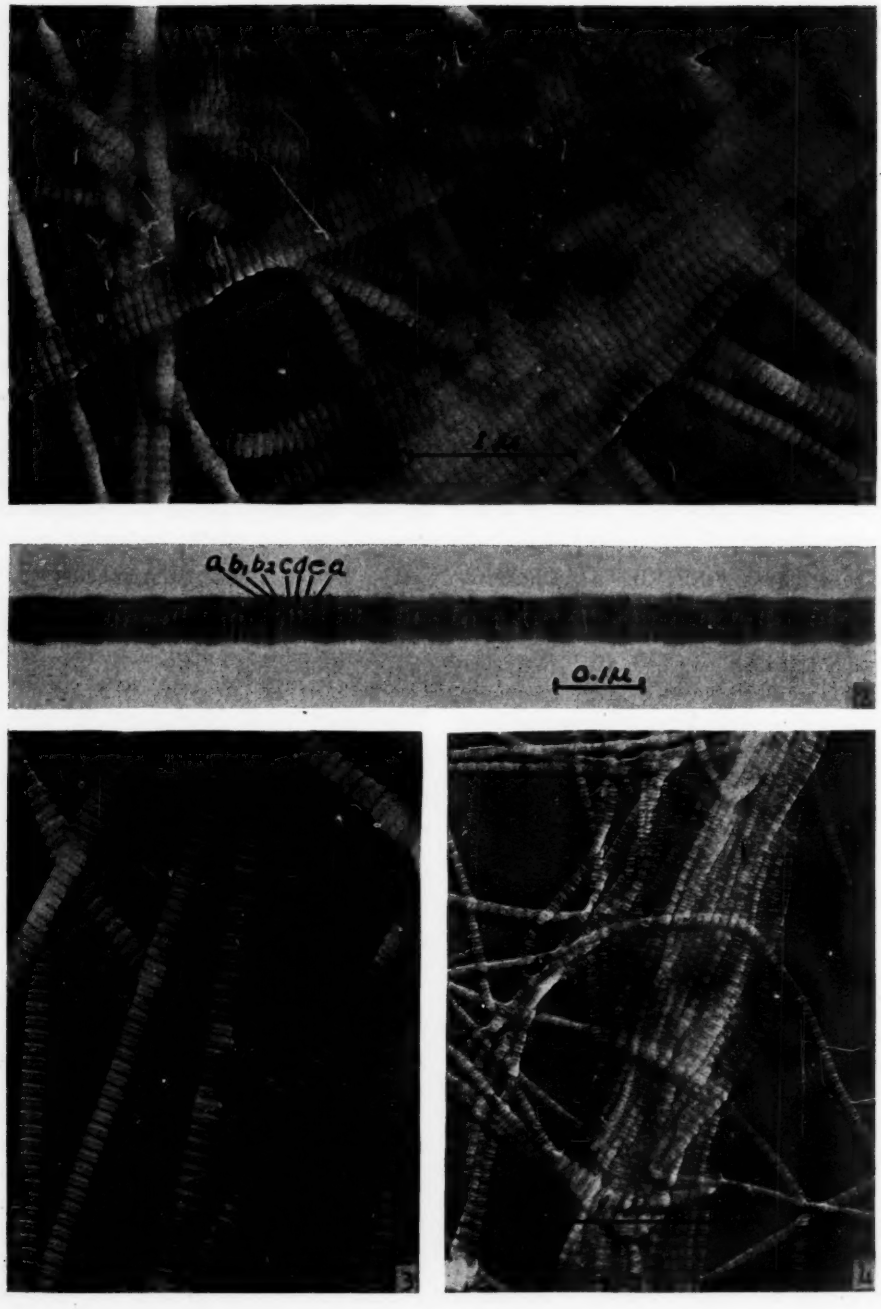

PLATE I

If these fibers are digested with trypsin and washed in water in the centrifuge one observes in the electron microscope large numbers of helically coiled threads and uncoiled filaments, singly and in pairs (figs. 7 and 8). Partially digested fibers are also seen (fig. 6). The relative numbers of coiled threads and uncoiled filaments varies with different preparations from the same tissue. The threads are extremely constant in thickness, averaging about 120 A and are composed of two intertwined filaments. The coils are always found tightly wound with an extremely constant pitch of about 530 A. The direction of coiling of the double helix is the same for all the threads of any one tissue. The threads of beef ligamentum nuchae elastin are all coiled clockwise—rabbit aorta in the opposite direction.

These threads and component filaments have been invariably found in all trypsin treated preparations of fish swim bladder, rat, rabbit, and cat aortae, bovine ligamentum nuchae, and skin of various mammals. Threads and filaments from these various sources seem to be morphologically identical. There was no obvious difference in appearance between these components from the aorta of an 85 year old arteriosclerotic and those of a 5 year old child. However, there may be a statistical difficulty here in that pathologic alterations may be focal and the largest proportion of the elastic tissue may be normal. A more careful study by microdissection of involved regions is needed.

Boiling the tissue prior to tryptic digestion did not destroy the threads; however, after having been liberated from the fiber by the enzyme they were heat sensitive. Coiled threads have not yet been seen in intact elastic fibers.

From this study, it was evident that the elastic fiber contains at least two components: a heat-resistant, trypsin-sensitive, amorphous matrix, binding together bundles of highly ordered, heat-sensitive, trypsin-resistant, fibrous units. What roles these two components play in the elastic behavior of the fiber is as yet unknown. Quantitative data on the relative amounts as well as the amino acid pattern of the two constituents are needed.

This problem has demonstrated an advantage of a direct visual examination of tissue fine structure over the indirect methods. The latter described only the over-all behavior of those tissue components present in appreciable amounts whose properties are measurable by the technique; structure is then deduced from the data.

Ground Substance.—The interfibrillar ground substance has given little evidence of organized structure detectable by methods at hand. It appears to be an amorphous gel which varies in amount and/or chemistry in the different species, tissues, and ages. There is considerable chemical evidence to indicate the presence of a complex of acid mucopolysaccharides and proteins (15, 88, 89, 98). The best known of the tissue polysaccharides are hyaluronic and chondroitin sulfuric acids (90); however, there is a good likelihood of others yet unknown being present. Unfortunately there is scant knowledge of the nature of the associated proteins or their chemical and physical relationships to the polysaccharides. Chemical analysis of hyaluronic acid reveals the presence of acetyl glucosamine and glucuronic acid in nearly equal proportions and of chondroitin sulfate, a sulfated acetyl galactosamine and glucuronic acid (58, 89). Phys-

FIG. 1: Bundles of collagen fibrils from human skin. Shadowed with chromium. 24,500X

FIG. 2: Collagen fibril from chrome tanned cow hide. PTA stained. Chrome tanning only accentuates the structure normally revealed by PTA staining. Six intraperiod bands are observed. 128,500X (From Schmitt and Gross, 118)

←

FIG. 3: Collagen fibrils from 90 day old rat skin. Filaments in background are released from elastic fibers by trypsin used to clean up this preparation. Chromium shadowed. 30,700X

FIG. 4: Bundle of collagen fibrils (reticulin) from 3 day old rat skin. Note similarity of axial fine structure and difference in fibril width from that of adult collagen. Chrominum shadowed. 30,500X

PLATE 2

FIG. 5: Elastic fiber from rabbit aorta prepared by boiling tissue to remove collagen (elastin is unaffected) and fragmenting with sonic waves. Chromium shadowed. 14,800X

FIG. 6: Elastin from rabbit aorta digested by trypsin. Partially digested fiber and released threads are seen. Chromium shadowed. 10,900X

FIG. 7: Elastin threads and filaments released from human aortic elastin and washed in centrifuge. Coiled threads and uncoiled filaments, singly and in pairs are observed. Chromium shadowed. 52,400X

FIG. 8: Elastin threads released by trypsin from cow ligamentum nuchae. Direction of coiling is same as in human aortic elastin threads, although opposite to those from rabbit aortae. Chromium shadowed. 57,000X

TABLE I. COMPARATIVE AMINO ACID ANALYSIS OF HIDE COLLAGEN, ICHTHYOCOL, SPONGIN, AND MAMMALIAN ELASTIN

Amino Acid	Cowhide (22) Gm./100 Gm. Protein	Ichthyocol (14) Gm./100 Gm. Protein	Spongin (17) Gm./100 Gm. Protein	Elastin (94) Cow Lig. Nuch. Gm./100 Gm. Protein
Total N.	18.6	....	13.0	17.1
Amino N.	0.46	....	....	....
Glycine	26.2	9.55	14.4	29.9
Alanine	9.5	14.7	0.2(33)	18.9
Leucine	3.2(94)	3.76	7.9	8.7
Isoleucine	2.1(94)	2.99	...	4.0
Valine	3.4	2.29	...	17.4
Phenylalanine	4.2	1.83	3.3	5.0
Tyrosine	1.4	0.0	0.8	1.61
Tryptophane	0.0	0.0	0.0	<0.01
Serine	3.4	4.13	...	.82
Threonine	2.4	3.22	...	.96
Cystine	0.0	0.1	2.8	0.15
Methionine	0.8	2.78	...	0.03
Proline	15.1	17.8	5.7(33)	17.0
Hydroxyproline	14.0	4.68	0.0(33)	2.0(126)
Lysine	4.5	4.35	3.0	0.39
Hydroxylysine	1.3	0.36	...	...
Arginine	8.8	9.33	4.3	0.89
Histidine	0.8	1.09	0.2	0.07
Aspartic Acid	6.3	4.72	4.5(33)	0.63
Glutamic Acid	11.3	8.19	18.4(33)	2.1
Amide N.	0.66	....	....	0.04(126)
Total Found	119.00	....	....	....

ical chemical studies suggest that in hyaluronic acid the molecule is a straight chain, high molecular weight polymer, and that the molecule of chondroitin sulfate may be branched (16). The question of branching, however, is still unsettled.

Polarized light studies of hyaluronic acid show positive uniaxial birefringence (16). The only roentgen ray diffraction study reported to date failed to reveal evidence of crystallinity (16).

Electron microscope examination of purified hyaluronate from umbilical cord indicates that the molecules are fibrous and polydisperse in length. There were no distinctive features in the drying patterns other than these (51).

In fibroblast tissue cultures Porter and Vanamee (107) have observed spindle-shaped fibrils having an axial period of about 1100 Å. They suggest that these are components of the ground substance but present little evidence to support the contention.

The Fibroblast.—The fibroblast synthesizes the stroma and probably controls its physiology to some extent. Fine structure studies of the fibroblast quite obviously have a different significance than the problem of the extracellular elements since they deal with the nature of protoplasm. They are correspondingly more difficult because of the extremely labile and dynamic state of the intracellular materials and organelles. Other than the electron microscope studies of Porter and associates on fibroblast cultures, very little has been done. Porter and associates have described a finely fibrillar and vesicular structure throughout the "hyaline" portion of the cytoplasm. Bang and Gey (6) observed long bundles of thin fibrils coursing through the cell, usually tending to parallel the free edges. These have also been observed by Porter (102) and Gross. Thus far little has been learned concerning the fine structure of mitochondria or the nucleus. Polarized light studies of mitochondria obtained from

parenchymal cells by fragmentation have only indicated the presence of fibrillar elements running parallel to the long axis of the structure (50). Phase contrast studies of kidney tubule mitochondria (142) indicate the presence of a mitochondrial membrane for which there is also some evidence from electron microscopy (35).

Summary

The over-all goal of fine structure analysis is to provide morphologic information in the molecular and colloidal realm which when combined with the data of analytic and physical chemistry will aid greatly in understanding biologic properties.

It has become increasingly evident that molecular and colloidal configuration are intimately involved in biologic specificity. This extension of morphologic study into the molecular range has imparted a dynamic aspect to a subject often considered to be reaching its limit of usefulness.

In this laboratory there are several long-range objectives in the fine structure study of connective tissue. The intent is: (1) to establish more precise definition of the constituents so that one may talk with confidence of specific entities; (2) to establish the intimate structure of the fibrous components of the connective tissue as part of an over-all interest in the nature of protein structure; (3) to study the genesis of these materials in an effort to gain some knowledge of the general problem of protein synthesis; and (4) to investigate the reactivity of connective tissue constituents in an effort to understand the physiology and pathology of the mesenchymatous tissues.

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Studies of Psychopathology in Later Maturity—A Review

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DR. GRANICK'S SURVEY OF THE LITERATURE ON THE PSYCHOPATHOLOGY OF LATER MATURITY REVEALS THAT BEYOND THE AGE OF 65 THERE IS A DISTINCT INCREASE IN EMOTIONAL DISORDERS, THE PRECIPITATING FACTOR OF WHICH IS FREQUENTLY INSECURITY. RECOVERY IN ELDERLY PATIENTS SUFFERING FROM MANIC-DEPRESSIVE AND INVOLUTIONAL PSYCHOSES IS NOT AS RAPID NOR AS COMPLETE AS IN YOUNGER PERSONS. EVEN IN THE OLDER AGE GROUPS, HOWEVER, COMPLETE RECOVERY MAY IN MANY INSTANCES BE ACCOMPLISHED THROUGH HORMONE THERAPY, SHOCK TREATMENT, AND PSYCHOTHERAPY.

THE increased interest of recent years in the psychology of later maturity seems likely to bring about considerable growth in the literature on the mental diseases associated with old age. A systematic search of reported research in the Psychological Abstracts and other sources reveals an amazing paucity of studies in the area to date. Descriptions of the diseases are found in the standard textbooks of psychiatry and abnormal psychology which are essentially based upon clinical reports rather than controlled experimental studies. In contrast, there is a relatively rich body of research which is generally referred to in discussions of the psychoses and psychoneuroses associated with younger age groups. A review of available research reports on psychopathology in later maturity thus seems advisable at this time to help set the stage for a systematic investigation of the field.

INCIDENCE OF MENTAL DISEASE

Later maturity and senility are apparently periods during which individuals are more likely to develop mental disease than at any other time of life. Malzberg (30) made a statistical analysis of 28,689 first admissions during a three year period to New York State mental hospitals and found the average age of admission to be 45.5 years. Rates of admission were shown to increase progressively with age from 0.7 per 100,000 population for children under 10 years to 420.2 per 100,000 people for individuals over 80. The chief diseases of old age appeared to be senile dementia, involutional melancholia, alcoholic psychosis, and psychosis with cerebral arteriosclerosis. Dementia praecox and manic-depressive psychosis tended to be found relatively more frequently in younger age groups. Over a five year period in one state mental hospital, Hoffman (22) discovered that 2.5 per cent of the admissions were patients with involutional psychosis. Of these only 26 per cent were males and 14 per cent manifested paranoid symptoms.

Studying the admission rate in relation to age of 61,161 first admissions to New York and Massachusetts mental hospitals from 1928 through 1932, Dayton (18) also reported a definite upward trend in mental diseases with increase in age, particularly above 65 years. Of interest in this connection is Overholzer's (41) observation that between 1910 and 1936 the number of admissions to mental hospitals of persons between 60 and 70 years increased 67.5 per cent. Post (44) similarly reported a general increase in the percentage of admissions of patients over 60 between 1903 and 1942 to the Royal Edinburgh Hospital in Scotland. In addition, Johnson's (28) statistical study of first admissions to one of the Pennsylvania state hospitals between 1910 and 1944 noted an increase from 11.6 per cent to 24.9 per cent of persons aged 65 and over.

Results comparable to those found by Malzberg were arrived at by Landis and Farwell (33) in their trend analysis of age at first

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admission to New York State mental hospitals between 1913 and 1941. They discovered, furthermore, that trends in Massachusetts and Illinois were roughly the same as in New York. Between 1910 and 1940 admission rates to civil mental hospitals in New York for groups between 20 and 59 years were found by Page and Landis, (42) to be fairly constant. Increase in bed capacity and old age psychosis, however, had brought about an actual increase in mental hospital population.

What the incidence of mental disease in the population actually is, however, cannot be clearly ascertained from the studies by Landis and Farwell and Page and Landis since only mental hospital cases have figured in the statistics. Some light is thrown on the subject, nevertheless, by Affleck's (2) report on psychiatric disorders among the chronically ill in hospitals. His survey of the hospital accommodations for the chronically sick in a city of 500,000 showed 758 patients of whom 80 per cent were over 65 years. Of this elderly group 37.3 per cent had some form of mental disorder. Farrar and Franks (18) supply further information by their statistical study of nervous disorders in relation to the menopause. On the basis of the 1929 figures on hospital admissions in a city with an estimated female population of about 47,000, aged 40 to 55 years, severe nervous disorders were found at the rate of 123 per 100,000 married women and 154 per 100,000 single women. These rates were considered to be no greater than those found among most other age groups.

It seems clear, generally, that old people are making increasingly greater demands on mental hospital facilities. Apropos is the conclusion arrived at by Lewis (25) from his recent study of first attack admissions to British hospitals for mental disease that within the next thirty years the bulk of mental patients can be expected to come from elderly groups of the population.

Abnormalities in Intellectual Functioning

Despite the fact that old people constitute a very large proportion of the mental hospital population, relatively little attention seems to have been devoted to the study of their intellectual functioning. Halstead (23) has attempted to develop a scale of 25 mental tests applicable to the senile age group which he administered to 18 senile dementia patients aged 70 to 83 years. All the tests were found to differentiate between the dementia and the standardization group, the latter manifesting better functioning. Eysenck (15) made an exploratory study of the mental organization of 75 senile dementia hospital patients (average age 73.4 years) by means of a factorial analysis of performance on 20 psychologic and motor tests. The observations showed the organization of mental functions of the subjects to differ markedly from that of normal adults, differential deterioration of abilities being evident. The senile group reflected the most pronounced deterioration in tests involving abstract reasoning, while the least deterioration appeared in tests involving reactivation of past experience and knowledge.

Cleveland and Dysinger (10) found, on the other hand, that a group of 20 senile psychotics, aged 64 to 83 years, were able to respond on

an abstract level to the verbal materials of the Wechsler Bellevue Intelligence Scale. There was, however, manifest a marked inability to respond to the nonverbal items and to the Goldstein-Scheerer Sorting Test on a conceptual or abstract basis. Another study reflecting the decrease in intellectual abilities accompanying mental diseases of old age was reported by Rabin (47), who administered the Wechsler Bellevue Scale to 150 hospital patients, aged 60 to 83 years, some of whom were psychotic. Total quantitative scores were found to be lowest in the individuals suffering from senile psychosis and arteriosclerosis.

Vocabulary functioning in senile psychotics was studied by Ackelsberg (1). Five types of word tests (synonyms, antonyms, categorization of words, word naming in given time limit, and homographs—subjects give different meanings to the same words) were administered to 50 senile dementia patients classified by the experimenter as least, mildly, and most deteriorated intellectually. Each test showed a progressive impairment in ability to deal with word meaning, thus contradicting the widely held hypothesis that vocabulary remained constant with mental deterioration. Along similar lines Feifel (19) tested 45 older emotionally abnormal subjects, aged 50 to 79, with the Terman Vocabulary Test and compared their responses to those of 68 younger abnormals, aged 15 to 29 years. The definitions given by the former group were qualitatively more immature, being close to the types of definitions given by children.

Indications of related differences between senile psychotics and normal adults were suggested by the results of a study of word usage in speech by Feldman and Cameron (20). Adjectives, regarded as a more complex speech activity than pronouns and verbs, were used relatively less often by the 28 psychotic patients than by the 17 normal adults investigated. Verbs and pronouns, on the other hand, were used with relatively greater frequency by the former group. In this the patient group was comparable to a group of 3 children with which it was compared.

Shakow, Dolkart, and Goldman (53) investigated the memory functioning of patients having senile and arteriosclerotic psychoses. The former showed poorer immediate memory ability than the latter on the Wells Memory Test, while both tended to perform at a lower level than normal subjects generally. Cameron (8) also found an impoverishment of immediate memory among a group of senile psychotics and pointed to a tendency on their part to elaborate memorized data, thus preventing proper retention.

Thinking processes in patients suffering from mental diseases in old age seem also to be less effective than those of normal adults. Eysenck (15) presented 24 perceptual problems to 100 male senile dements. Their scores were in all cases below the average of adults. Of interest particularly was the finding that no differences between the patients and normal adults appeared in errors made, but there was a significant difference in time taken to do the problems. Along somewhat different lines Cameron (9) compared the thinking of 22 senile psychotics with 25 schizophrenic patients, 29 children, and 20 normal adults on their responses to four incomplete sentences involving casual relations. The performance of both psychotic groups was judged to be inferior to the children and normal adults. On the other hand, the senile subjects were superior to the schizophrenics in their use of language for communication. Furthermore, the former group showed a better retention of social orientation and critical capacities than the latter.

Available evidence, therefore, suggests the presence of severe intellectual deterioration in patients of advanced age suffering from mental disease. The decrease in abilities involves language, motor, memory, and abstract thinking functions to the point that the performance of the average person with senile dementia, arteriosclerotic psychosis, and schizophrenia of long duration appears to be little better than that of young children.

Abnormalities of Personality Functioning

The high proportion of mental disorders among older adults suggests that the problems of adjustment during this life period are relatively severe. Diethelm and Rockwell (14) studied 110 psychiatric patients over 45 years of age and reported that the outstanding dynamic factor in the personality breakdown was insecurity. The outstanding psychopathologic reactions noted were anxiety, depression, and paranoid feelings.

Problems faced by people in later maturity which seem to heighten emotional stress and lead to personality disorganization were found by Prout and Bourcier (45), on the basis of a study of 100 psychiatric hospital cases aged 40 to 60 years, to be related to support of family, social and communal obligations, economic security, biologic involution, curtailment of physical activity, and fears over sexual potency. The same difficulties seemed to affect adversely the emotional stability of individuals who did not develop clear-cut mental diseases. Thus, Woltman (62) found little correlation between intensity of clinical disability and extent of pathologic changes in 200 patients over age 60 who had been referred for neurologic examinations. Indicated was a high incidence of neurosis related to frustrations resulting from early retirement, dependency, and social isolation.

A relationship between life experiences and the development of emotional disorders in old age is suggested by most studies on the personality functioning of senile groups. That the pre-psychotic personalities of such people may well be an important factor in the development of mental disease by individuals faced with the problems of adjusting to old age is indicated by Titley's (56) study of the social and psychiatric histories of 10 patients, aged 50 to 61 years, manifesting involutional melancholia. They are shown to have the following traits: narrow range of interests, difficulty in adjusting to change, limited capacity for sociability, rigid adherence to high ethical standards, proclivity for saving, reticence, anxious tone, stubbornness, over-conscientiousness, and meticulousness. Similar results were reported by Hamilton and Ward (24) in their study of 100 women patients suffering from involutional psychosis.

Further light is thrown on this subject by Semrad and McKeon (53), who investigated the social histories of 14 mental patients over 70 years of age committed to a hospital for the first time. Most of them had long histories of personality difficulties and financial dependency. An important precipitating factor in the breakdown was the removal of protective support when their original home environments were disrupted.

Racial or ethnic background was shown by Klopfer (30) not to be a factor in the development of mental diseases of old age by means of a statistical study of admissions to New York State and Massachusetts mental hospitals. Life situations and experiences were stressed as contributing causes. Williams, Quesnel, Fish, and Goodman (60) showed similar factors to be involved in a careful clinical study of a group of 47 senile dements. On investigating a comparable group of arteriosclerotic psychosis patients they concluded that, whereas senile dementia arose in a characteristic setting of either denial or failure to achieve social integration and financial independence, personality factors seemed insignificant in the latter disease.

Clow (11), however, reached a different conclusion regarding psychotics with cerebral arteriosclerosis, following his clinical study of 100 cases. Toxic factors, he found, accounted for only some of the personality breakdowns, but emotional disturbances were the most frequently involved contributing causes. Abnormal anxiety and tension in adult life, narrow interest range, and sexual maladjustments were outstanding characteristics.

Further evidence along these lines is contributed by two studies of the menopausal syndrome in women. Stern and Prados (55) examined 50 cases diagnosed as menopausal

syndrome psychiatrically by interview, social history, and the Rorschach Test. They found a uniform picture of a reactive depression which represented an accentuation of previously existing maladjustments. Greenhill's (22) comparison of 100 women manifesting the menopausal syndrome with 50 who had shown no psychoneurotic symptoms during menopause also led him to conclude that the subjects of the former group had been emotionally disturbed for most of their lives.

Depressions seem to occur quite frequently in people approaching old age and have been the subject of a number of investigations. Brockhausen (7) studied 201 female cases of involutional depression genetically and found an etiologic distinction between depressive psychosis occurring in the involutional period for the first and only time and the periodically recurrent form of involutional melancholia. Social and family histories of the two groups were markedly different. Malamud, Sands, and Malamud (37) reported that the climacterium plays an important role in the development of involutional psychosis. From a study of 47 patients between 42 and 64 years of age, confirmed by a follow-up investigation eight years later (38), it was noted that adjustment to involution was made difficult by an inflexible personality structure and by experiences of a catastrophic nature which threatened the individual's personal and social security.

Related to these findings is the study of the expressed mental condition of 300 involutional patients by Saunders (50). Noted particularly were ruminations of loss, self censure, regret, guilt because of neglected opportunities in the past, doubts about the present, and feelings of personal inadequacy toward the future. Doty (15), who studied 25 manic-depressive patients, also stressed poor personality and disturbed family background as factors in the development of the psychosis after the age of 40 years.

The age at which individuals develop manic-depressive psychosis and other emotional disorders in later maturity seems of some importance in relation to speed of recovery. Thus, Malzberg (39), in a survey of manic-depressive cases admitted to U. S. mental hsopitals during 1922, found that the patients of advanced age recovered somewhat more slowly than the younger patients. Clow (12) similarly discovered a relationship between age and capacity for recovery in functional mental disorders of later maturity. In his study of 365 mental patients above 60 years of age admitted to a New York hospital during a ten year period, 64.9 per cent had functional type reactions and 35.1 per cent manifested organic impairments. Of these 64.1 per cent either recovered or improved and 14.5 per cent died in the hospital. The organic disturbances showed little improvement, but the functional disorders, particularly the manic-depressives, tended to recover. Furthermore, the incidence of recovery was generally greater among the younger patients.

Speed and maintenance of recovery by older patients was found to be related also to prior personality adjustments by Maclay and Whithy (36). In treating 100 men and women, average age 45 years, for psychiatric problems percipitated by the war, they found that the prolonged cases had long-standing emotional difficulties in contrast to those who recovered quickly. Furthermore, the older patients were most markedly affected by the stress of war. Observations by Shorr (54) on several hundred menopausal women in a general hospital who manifested various associated physiologic and psychologic disorders pointed in the same direction. Those patients who had histories of marked personality maladjustments failed to respond to hormonal treatment in contrast to the satisfactory responses of the previously well adjusted individuals.

Anderson (3), on the other hand, regarded persons suffering from depressions of later life, even when dementia is not present, as having a generally poor prognosis. Of the 50 women, aged 41 to 74, studied, only about a third recovered. The duration of illness for the patients who recovered was from fourteen to forty-two months, which agreed closely with previously reported findings by Hoch and Mac-

Curdy (25) who observed 67 cases of involutional melancholia over a period of more than four years.

Personality functioning prior to the onset of a depression in later life was also regarded by Anderson (3) as being of little prognostic value with reference to recovery or response to treatment. The observations by Haynes and Jacobs (26), however, would suggest that the depth and duration of the disturbance are important factors in this regard. Of the 30 patients with involutional psychoses given shock and endocrine treatment, those having relatively short histories of personality disturbances benefited most. In addition, when paranoid or schizophrenic symptoms were present, suggesting long-standing, deep-lying disturbances, treatment was found to be ineffective. Here again there was agreement with observations by Hoch and MacCurdy (27), who indicated that involutional melancholic patients recover "unless they show marked insufficiency of affect, peevish or autoerotic behavior, or ridiculous hypochondriacal delusions which usually are concerned with the alimentary tract."

The question as to whether treatment generally is effective in the mental disorders of later maturity has been the subject of a number of studies. Relief of constitutional symptoms through hormonal treatment of 30 cases of depression and anxiety in middle-aged men was reported by Prados and Ruddick (45). Deep psychotherapy or electric shock was, however, required in those instances in which psychologic disturbances were severe. In another experiment (57) involving 41 involutional melancholia patients, 21 were treated with theelin while the rest received normal saline. While none of the latter group improved, several cases in the experimental group experienced relief of symptoms. Several follow-up studies by the same authors (4, 58, 59) led them to assert, after some modifications of their treatment technique, that the recovery rate for uncomplicated involutional melancholia patients treated with theelin was 90 per cent.

Shorr (54), Jones, MacGregor, and Tod (31), and Hawkinson (23) are among a number of other research workers whose clinical studies further indicated that hormonal treatment tended to bring about improvement in patients manifesting depressive reactions associated with the menopausal period. Hawkinson's study seems particularly important since it involved 1000 consecutively treated patients.

Schube, McManamy, Trapp, and Houser (51), however, in a careful study of 10 such cases treated with theelin found no significant improvement. Similarly, Palmer, Hastings, and Sherman (43) found estrogen therapy totally ineffective with 11 involutional melancholia patients. These authors suggested that the endocrine imbalance is but one contributing factor in the emotional breakdown of such subjects. Their deeply rooted pathologic personality traits were regarded as being of greater significance. It seems possible, on the basis of these and other related reports, such as those by Bowman and Bender (6) on 7 cases, and by Ripley, Shorr, and Papanicolaou (48) on 20 cases, that hormonal treatment is effective in relieving the symptoms of the disturbance, thus making the patient more comfortable and at ease, but that no essential personality changes are brought about.

Shock or convulsive treatment for cases with involutional psychoses seems to have proved effective according to a number of reports, only some of which are reviewed here. Many others are discussed by Fishbein (21). Of 24 such cases treated with metrazol by Bennett (53), 23 recovered or improved. Wilson (61) obtained similar results with 16 out of 19 patients, as did Palmer, Hastings, and Sherman (43) with 19 out of 27 individuals. Along the same lines, Robinson (49) used metrazol on 36 cases of affective disorders in people passed the age of 60. Thirty-three recovered sufficiently to be able to leave the hospital.

Electric shock was used by Huston and Locher (29) on 61 involutional psychotics and the results compared with the spontaneous recovery rate of a group of 93 untreated subjects. Recovery or improvement was shown by only 46 per cent of the latter group in contrast to 80 per cent of the shock group. Simi-

larly, Fishbein (21) compared 347 such patients given electric shock treatment with 61 treated by other methods. Of the former group 57.6 per cent recovered, but only 24.5 per cent of the latter group was restored to good health.

Lovell (35) also had success in treating depressive reactions of old age with electric shock. The patients, however, who manifested schizophrenic, delusional, or organic symptoms failed to respond satisfactorily. It was emphasized, in addition, that for maintenance of the improvement brought about by shock, psychotherapy was advisable. The study by Hamilton and Ward (24) similarly pointed to the need for applying a multi-therapeutic approach to the handling of involutional psychotics. Of 100 women given psychotherapy only 42 per cent benefited. On the other hand, when psychotherapy followed electric shock, 75 per cent of a group of 69 patients recovered. Along the same lines, Haynes and Jacobs (26) applied shock, endocrine therapy, hydrotherapy, occupational therapy and psychotherapy to their 26 involutional psychotics and found that those whose disturbances were of relatively short duration and who did not manifest paranoid and schizophrenic symptoms were benefited significantly.

By and large, most of the available studies on the characteristic psychopathologies of later maturity and old age seem to indicate that those who develop severe mental disturbances are people whose personality adjustments have been poor for a good proportion of their lives. Feelings of insecurity and severe anxiety, as well as depression and emotional lability, are reported to be the outstanding symptoms accompanying these diseases. The breakdown apparently is precipitated by such factors as loss of financial support, inability to be productively active, and feelings of impotence towards meeting new adjustment problems. Many patients recover spontaneously from their affective disorders. It seems, however, that treatments with hormones, electric or metrazol shock, psychotherapy, and related methods are effective in speeding recovery and increasing the number of those who become socially and emotionally competent.

Summary

A review of available research literature related to various aspects of psychopathology associated with later maturity and old age indicates the following general trends.

Associated with the increase of the total number and proportion of old people in the general population is found a marked increase in demand on the part of this age group on available mental hospital facilities.

The incidence of mental disease for people between the ages of 40 and 60 does not seem to be very much greater than that for most other age groups. Beyond the age of 65, however, there is a marked upward trend of serious emotional disorders with increase in age.

Severe intellectual deterioration is suggested by research studies on patients of advanced age suffering from mental disease. Language, memory, motor, and abstract thinking functions are involved.

The outstanding factor in personality breakdown in old age seems to be insecurity. Reactions generally found are anxiety, depression, paranoid feelings, ruminations of loss, self censure, regret, doubts about the present, and feelings of personal inadequacy toward the future.

Personality disorganizations in the involutional period and old age seem to be related in large measure to previous poor social and emotional adjustments. Problems of adjustment to old age which may precipitate emotional breakdowns include particularly inability to support one's family, failure to meet communal and social obligations, lack of economic security, and inadequate biologic functioning.

Recovery from manic-depressive reactions and involutional psychoses which occur in middle life and later maturity is found to be more rapid and complete in relatively younger patients. Subjects manifesting comparatively severe symptoms of a schizophrenic or para-

noid nature and those whose illness is of long duration tend to have a poor prognosis.

Hormone treatment for involutional melancholia and menopausal syndrome seems effective at least in relieving symptoms and thus making patients more comfortable and at ease. Personality changes leading to full recovery seem more likely to ensue if electric or metrazol shock and psychotherapy are used to supplement each other.

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Nonresident Aid—Community Versus Institutional Care for Older People

RUTH LAVERTY

A STUDY OF THIRTY ELDERLY WOMEN, FIFTEEN OF WHOM WERE ADMITTED INTO A HOME FOR THE AGED AND FIFTEEN OF WHOM WERE PLACED ON A NONRESIDENT CARE PROGRAM DISCLOSED THAT THOSE ON NONRESIDENT AID WERE BETTER ADJUSTED AND ALSO WERE BETTER ABLE TO ADJUST TO CARE IN THE HOME WHEN ADMITTED. IN ADDITION THE COST OF CARING FOR THE NONRESIDENTS WAS MUCH LESS THAN THAT FOR THE INSTITUTIONALIZED GROUP. THIS PAPER WAS PRESENTED AT THE SECOND ANNUAL SCIENTIFIC MEETING OF THE GERONTOLOGICAL SOCIETY IN CHICAGO, NOVEMBER 5-6, 1949.

PEOPLE at any age continue to have the same basic emotional needs as in early life. The opportunity to satisfy those needs becomes increasingly difficult in later years, particularly in our culture where age finds itself competing with youth for a livelihood and where so many of the aged have outlived their friends and relatives. The insecurity of their position tends to make the elderly an exceedingly anxious group.

Some of the financial strain is eased through public assistance, but what channels are there for supplying the more intangible values in life? How can the aged be made to feel wanted and useful when they cannot be part of a family? How can they be given approval and encouragement for their efforts when there is no medium through which they can be productive? How can they be creative or achieve recognition when society has no real place for them? Is there an effective method of giving enough psychologic sustenance to offset society's destructive attitudes?

These questions are challenging ones, and a number of social organizations throughout the country have taken up the challenge, each approaching the problem in a different way.

One social agency in New York City, the Peabody Home for Aged Women, has developed a program of community service specifically designed to meet both the physical and emotional needs of the aging, but not-yet-old, portion of the population. The need for this type of service arose from the institution's concern over the large number of applicants rejected annually because of space limitations.

Over a four year period there were more than 2,000 applicants, with only 20 vacancies occurring within the Home. One per cent could be cared for, but what about the other 99 per cent? All other homes for the aged were asking the same question. When the reasons given by the old people for applying for institutional care were studied, it was found that financial need, housing problems, fears relating to mild present ailments or possible future illness, poor family relationships, and loneliness, consistently made up about 85 per cent. None in this group needed immediate institutional care. A large percentage preferred independent community living, but dwindling resources compelled them, against their will, to apply for admission into an old age home.

If the needs of these older people could be met in a way that would help them to continue their usual manner of life in the community and at the same time give them full assurance of future care at such time when it was needed, it was believed that pressure for placements in the Home would be greatly relieved. With this aim in view, the Nonresident Aid program, to differentiate it from the care given to residents within the Home itself, was established in 1945. In essence, the plan is a combination of the in-

Mrs. Laverty received her B.A. degree in Sociology from New York University in 1941 and her M.S. degree in 1943 from Columbia University and the New York School of Social Work. From 1943 to 1945 she did medical casework for the Presbyterian Hospital, New York, and since 1945 she has done geriatric casework and is Director of Social Service and Field Director, Peabody Home for Aged Women, New York. She was also lecturer in social work at Queens College, New York City in 1949 and is now lecturing at New York University, New York City, on Aging in Contemporary Life.

stitution's services and community resources extended into the old person's home.

An experimental group of 15 women who met the admissions requirements of the Home were selected from the regular application list and accepted as nonresidents. They were given full assurance that they would be admitted into the Home at such time when they were no longer able to look after themselves. Another control group of 15, chosen from the same source and by the same criteria, were admitted directly into the Home. Every effort was made to pick 30 women of about the same cultural background to form as homogeneous a group as possible. These people were in financial need and had no close relatives whom they could call upon for help in case of emergency. Consequently they were beset with many fears and anxieties whose source originated from their insecurity. They were given a thorough physical examination by the Home's physician and were all adjudged to be in reasonably good health, mentally alert, and able to give complete self care. The ages ranged from 65 to 80 in both groups, with the average age differential between the two groups proving to be only a little over one year.

The residents at the Home under institutional care were freed from all normal anxieties. Nursing and medical care was immediately available on the premises in case of need. The building, a modern one, provided each woman with her own private room, comfortably and attractively furnished by the Home or with her own things, whichever she preferred. Well-planned recreational and occupational therapy activities took care of their leisure hours. They were permitted full freedom to go and come as they pleased and to have visitors at any time or on any day. The standards of the Home are exceedingly high, and the general atmosphere is a cheerful, comfortable, and decidedly noninstitutional one.

The nonresidents were also relieved of all anxiety, but they carried full responsibility for their own care. Financial need was alleviated either through public or private assistance. The Home also gave monthly money grants for necessary items which could not be supplied by any other source. All community resources were used in behalf of their welfare. Partial or full employment or volunteer work was encouraged. The women lived in furnished rooms or small apartments and did their own marketing, cooking, cleaning, and recreational planning. Preventive medical care was strongly emphasized. Visiting nurse service, private physicians, district clinics, and hospitals were used as needed. Nonresidents were considered members of the Peabody family and were invited to all major social events at the Home.

Contact between the Home and the community group was also maintained through the regular visits of the social caseworker who called on each nonresident at least once a month or more often as circumstances demanded. She was also available on call between visits to help each nonresident resolve whatever difficulties may have arisen in the meantime. Old people living alone tend to become more easily disturbed than younger age groups when unforeseen events upset their usual routine. Therefore, they are particularly in need of an interested, dependable source to whom they can turn for help or counseling in times of trouble. The caseworker, as the representative of the Home, supplies that need for reassurance.

Casework methods and techniques were used with the primary objective of helping each individual effect as great a degree of independence and as good a social adjustment as her limitations allowed. Through the therapeutic

casework process, ego strengths were evaluated and utilized constructively by directing them into satisfying activity. Supportive casework therapy (1) was especially successful in revitalizing emotional and physical energies of those who had broken under the weight of their adversities.

One case is particularly illustrative of a woman who, mentally and physically exhausted by the insecurity of her situation, was on the verge of a mental breakdown and would have become a total burden on the community:

> At age 65 Mrs. A. applied for admission into the Home. She stated her situation as "too worried to know what to do, and too wearied to do it, even if I knew what." Her physical health was poor because she had tried "to live on too little for too long." She suffered from many vague ailments, mostly of neurotic or psychosomatic origin. Mrs. A. was accepted as one of the 15 nonresidents in this program. Her medical and material needs were immediately taken care of through the proper channels, and her emotional needs were also met, much more gradually, of course, through the casework relationship.
>
> Given sufficient assurance that both the caseworker and the agency she represented could be called upon for help in case of emergency, coupled with generous encouragement and approval for her efforts, this woman was able to mobilize her energies into the direction of self help. Within three months, she obtained a clerical job on her own volition, despite the fact that she had no particular work experience to offer. She managed to hold her job satisfactorily for four years and then was replaced by younger help. Within two months, Mrs. A. was recalled because her employer had found that in comparing her four year record with the brief ones established by younger workers who succeeded her in that job, Mrs. A.'s report indicated surprisingly little absenteeism, much more dependability, conscientiousness, and steadier performance.
>
> This period was not without many difficult episodes. Whenever things went wrong at the office, Mrs. A. became panicky and wanted to leave, but she usually consulted her caseworker first. She was sure she was blamed for other people's mistakes; she thought she was given the hardest and worst jobs to do; she didn't think her employer appreciated her hard work. Each time, the caseworker helped her through these difficult periods by giving her the praise and approval her employer did not, by assuring her that the agency would see to it that she was not left destitute, by helping her to face the realities in each instance and to differentiate them from imagined persecutions.
>
> To sum up this case briefly, Mrs. A. is still employed and fully self maintaining, at an estimated total saving to the taxpayer of approximately $5,000.

After a two year period, the resident and nonresident groups were compared. The findings are enlightening and should prove of particular significance to organizations interested in the development of services or programs for the aged.

Physically: The medical reports revealed that the nonresidents as a group, all of whom were still living, maintained better health than the control group in the Home. The general pace and tempo of the experimental group seemed noticeably faster than that of the control group in the Home. More than half were even in better physical condition than when they were originally examined at the time of acceptance, even though they were two years older. Three women, all over 80, began to show signs of excessive physical fatigue due to the strain of self care, and these 3 were admitted into the Home shortly thereafter. All 3 made easier and quicker adjustments to congregate living than did any one of the 15 residents in the control group in the Home, of whom 12 were still alive. The period of community living provided a natural opportunity for these women, through regular contact with the caseworker, to become conditioned to the kind of life they would lead in an institutional environment, without injury to their sense of pride or infringement upon their feelings of personal liberty.

Emotionally: The nonresidents seemed to be a much happier group. Their conversations with the caseworker indicated a decided trend towards externalization of interests. They were alert to local and world affairs and participated enthusiastically in neighborhood and church activities. Their relationship with friends, neighbors, employers, and other people with whom they were in contact was good. There was little or no evidence of self pity,

and they showed a strong desire to be helpful to others. Even more interesting, they did not think of themselves as old, yet frequently referred to the resident group as "those poor old ladies at the Home." Their activities were normal and healthy, and their planning was in terms of the present and future, all of which make for good mental hygiene.

Conversations between the caseworker and the residents, on the other hand, pointed to a pattern of internalized interests with excessive preoccupation with self. They tended to exaggerate minor ailments and were given to much self pity. Hoarding, criticism of their neighbors, constant demands for attention, suspicions, strong rivalries, resentment and resistance against even slight deviations in routine, and reluctance to participate in the Home's activities were some of the more common reactions noted. They thought of themselves as very old ladies, liked to have everything done for them, and spent much time in planning for their funerals.

This comparison does not imply that the nonresidents had all the virtues and residents all the vices, but in terms of degree of the observable positive and negative aspects of behavior, the nonresidents by far made better personal and social adjustments to their respective situations and environments. They had learned, as nonresidents, how to be self reliant, and the carry-over of this experience was of inestimable value when they eventually were admitted into the Home.

It is interesting to note that even after nonresidents entered the Home, a narrowing of interests and a regressive pattern to infantile reactions became apparent. The very nature of an institutional environment seems to nourish dependency feelings and to bring forth the kind of behavior reactions that develop into early senility, even in a Home like Peabody where an informal, homelike atmosphere prevails.

Financially: Nonresidents handled their budgets, limited as they were, in a much more realistic fashion. None exceeded their monthly grants or earnings, and none made any requests for additional money, despite rising living costs, except for necessary nonrecurring items not estimated in their budgets, such as unusual dental or medical care, or heavy winter clothing. They took pride in balancing their budgets and even managed to save a little towards a much-wanted luxury or for trainfare to visit out-of-town friends. Even when a small gift of money was occasionally offered to them, several requested that it be given to someone needier than themselves.

The resident group was allowed up to $15.00 monthly for pin money, according to the Home's policy. Some spent their allowances quickly with evident lack of planning to make their money last through the month. Since the Home provides adequately for all their needs, they had no necessary expenses, yet they complained of the high cost of living and openly hinted that they would like larger allowances. Their behavior approximates that of children who are not too close to reality and who look to their parents to supply all their needs and whims, even to the point of indulging in "ladylike tantrums" to get what they wanted in the way they wanted them.

From the Home's point of view, the cost of the nonresident program is an exceedingly economical one. Figures, especially if expressed in dollars and cents, can be very graphic. Quoting current figures, the average cost to the Home for each nonresident is $16.56 a month. The per capita cost of each Home resident is $125.00 a month. It is estimated that one full-time caseworker can service 40, possibly even 50 nonresidents, provided that all her time is devoted to them and not drained off by other duties; whereas a staff of 20 people is needed to care for the 50 residents in the Home. As indicated previously, full utilization of personal resources, which include rehabilitation for employment, plus community resources, produces dollar economy in the care of older people.

The two groups were compared at the end of three years and again after the fourth year.

The findings are essentially the same. The Nonresident Aid plan sponsored by Peabody Home for Aged Women, is now in its fifth year of operation. Since rehabilitation of the elderly through geriatric casework is remunerative not only in terms of human happiness but in actual dollars as well, the program is currently being expanded to double the number of women under care.

Although Nonresident Aid is far from being the perfect formula for relieving all anxiety in the aged, yet this plan seems to possess many of the elements needed to effect emotional security in that portion of the population that is most neglected by our society.

Summary

The conclusions drawn from this study stand out clearly:

Casework method in meeting the basic emotional needs of the aged is a successful rehabilitative approach.

Mental and physical deterioration may be retarded by encouraging normal community living for older people as opposed to premature institutional admission.

Institutional placement is far more costly than a home care service; therefore, protective supervision should be considered only for those who are no longer capable of self care.

Assurance of eventual Home admission when in need of institutional care relieves fears related to future illness, tends to eliminate pressure for immediate admission, and gives the aged a feeling of security.

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HISTORICAL SECTION

GIOVANNI BATTISTI MORGAGNI (1682-1771)—distinguished Italian physician, published the results of his life work in his seventy-ninth year, in *De Sedibus et Causis Morborum*. Here for the first time in medical history clinical and post mortem observations were correlated in a large number of cases by a clear-thinking observer. By describing many new forms of disease, Morgagni, according to Garrison, made pathology a genuine branch of modern science.

His book abounds with cases of disease in the aged, emphasizing particularly such conditions as cataract, cerebral hemorrhage, phthisis, pneumonia, lung abscess, arteriosclerosis, calcification of the aorta, and the first recorded case of heart block, as well as many instances where trauma was the cause of death.

F. D. Z.

CURRENT COMMENT

News and Notes

At the annual meeting of the American Psychological Association in State College, Pennsylvania, September 2-8, 1950, the Division on Maturity and Old Age sponsored many papers and symposia featuring current psychologic research in the field of gerontology. Discussion sections included the following general topics: intelligence and aging, adjustment in aging, personality in aging, the measurement and significance of mental deterioration, and suggestions from child development studies for research in maturity and old age. The president of the Division, Dr. George Lawton, delivered an address entitled Psychotherapy in Middle and Late Maturity.

An interesting trend was revealed in the report of the Membership Committee that application for membership to the Division had increased 30 per cent over last year's figure, pointing up the general increase in interest in the problems of aging among psychologists.

A Conference on Aging, sponsored by the Social Science Research Council, was held at the University of California, Berkeley, California, August 7-10, 1950. Dr. Harold E. Jones was General Chairman, and the conference followed a two months' Institute on Aging at the University of California conducted by Dr. Jones.

The program of the conference was divided into four sections:

Survey of Current and Projected Research
Lloyd Fisher, Chairman

Biological and Social Factors
Agnes Morgan and Roy M. Doran, Chairmen

Methological Problems
William Stephenson, Chairman

Administration Problems
Oscar Kaplan and Frank Newman, Chairmen

An Institute on Geriatrics was held September 11, 12, and 13, 1950, at Loyola University, Chicago, sponsored by the Department of Public Health Nursing. Miss Margaret Ranck, consultant nurse, Division of Hospital Construction and Services, Illinois Department of Public Health, presided.

The American Occupational Therapy Association will hold its national convention at the Hotel Colorado, Glenwood Springs, Colorado, October 16-21, 1950. Miss Marjorie Ball, Miriam Rehabilitation Hospital, Webster Groves, Missouri, will be moderator of the section on geriatrics.

The establishment of the JOURNAL OF GERONTOLOGY was made possible by a grant from the Josiah Macy, Jr. Foundation.

The hieroglyphics, "The Beginning of the Book for Transforming an Old Man into a Youth," at the top of this editorial page, are from the Edwin Smith Surgical Papyrus, translated by Professor John Breasted, University of Chicago Press.

The 1950 Convention of the Association of Military Surgeons of the United States will be held from November 9 to 11, inclusive, at the Hotel Statler, New York City. The program will deal with civil defense, the defense role of the physician, aviation medicine, rehabilitation, military medicine, surgery, sanitation, and discussions on the use of the newest therapeutic and prophylactic agents in emergency conditions.

The program of the 117th Meeting of the American Association for the Advancement of Science, to be held in Cleveland, December 26-30, 1950, will include sections on chemistry, zoological sciences, psychology, social and economic sciences, medicine, dentistry, and pharmacology.

The seventy-eighth Annual Meeting of the American Public Health Association and meetings of 32 related organizations in the field of public health and preventive medicine will be held in Kiel Auditorium, St. Louis, Missouri, October 30 to November 3. More than 400 speakers and discussionists are expected to participate in the scientific programs under development by the thirteen Sections—Dental Health, Engineering, Epidemiology, Food and Nutrition, Health Officers, Industrial Hygiene, Laboratory, Maternal and Child Health, Medical Care, Public Health Education, Public Health Nursing, School Health, and Statistics.

The Third Annual Institute on Living in the Later Years, held at the University of Michigan in Ann Arbor June 28-30, maintained the high standards established by the two previous institutes. Attendance surpassed that of previous years in number and in geographic distribution, and there was also a diversity of interests in the representation of both professional and lay groups.

The members demonstrated a growing capacity to take advantage of the Institute by supplementing the carefully planned program with spontaneously formed sessions to discuss related topics. A panel discussion on the Rewards and Penalties of Growing Older, provided by the retired citizens of Ann Arbor, and a demonstration of the Activities Center, presented by an organized group of older people who meet regularly in Ann Arbor, were both considered valuable and interesting to the members of the Institute.

ORGANIZATION SECTION

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Program of the Third Annual Scientific Meeting of Gerontological Society, Inc.

Saint Louis, Missouri
November 12 and 13, 1950

Sunday, November 12, 1950
Morning Session

8:30 - 9:00 a.m. Registration. Elliot Auditorium, Oscar Johnson Institute, 640 South Kingshighway.

9:00 a.m. **Symposium—Studies on Arteriosclerosis.**

Robert A. Moore, Chairman

Paul D. White, Boston, Massachusetts. **Clinical Aspects.**

W. Stanley Hartroft, Banting and Best Institute of Medical Research, University of Toronto, Toronto, Canada. **Experimental Renal Hypertension of Dietary Origin.**

Henry S. Simms, Department of Pathology, College of Physicians and Surgeons, New York, New York. **A Review of Research on Lipfanogens and Antilipfanogen.**

Forrest Kendall, Goldwater Memorial Hospital, New York, New York, **Lipid Metabolism.**

A. I. Lansing, Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri. **Aging of the Arterial Wall.**

Charles A. Woerner, Department of Anatomy, University of Louisville School of Medicine, Louisville, Kentucky. **Microscopic Anatomy of the Arterial Wall.**

John Esben Kirk, Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri. **Metabolism of Arterial Tissue.**

12:00 noon Meeting of the Council of Gerontological Society, Inc.

Afternoon Session

Robert J. Havighurst, Chairman

2:00 p.m. College Professors in Retirement, Elon H. Moore, Department of Sociology, University of Oregon, Eugene, Oregon.

2:20 p.m. Counseling and Guidance Service for the Aged. Ruth Laverty, Peabody Home for Aged Women, New York, New York.

2:40 p.m. A Comparison of Factors in the Personal Adjustment of Old People in Protestant Church Homes for the Aged and of Old People Living in

Public Institutions. Ju-Shu Pan, University of Chicago, Chicago, Illinois.

3:00 p.m. Social Roles and the Prevention of Senility. Ruth Albrecht, Committee on Human Development, University of Chicago, Chicago, Illinois.

3:20 p.m. The Meaning of Work in Relation to Retirement Policy. Robert J. Havighurst, Committee on Human Development, University of Chicago, Chicago, Illinois.

3:40 p.m. Psychiatric and Group Therapy and Case Work in Support of Diabetic Treatment. Julius Weil, Montefiore Home, Cleveland, Ohio.

4:00 p.m. Business Meeting of Gerontological Society, Inc.

7:00 p.m. Reception and Dinner, Hotel Chase.

Presidential Address—C. J. Van Slyke, Director, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

Monday, November 13, 1950
Morning Session

Nathan W. Shock, Chairman

9:00 a.m. A Comparison of Aging Processes in the Pulmonary Artery and Aorta. H. T. Blumenthal, Fred P. Handler, Jack Zuckner, and S. H. Gray, Department of Pathology, St. Louis University School of Medicine, Laboratory of the Jewish Hospital, and Snodgras Laboratory, City Hospital, St. Louis, Missouri.

9:20 a.m. Diuresis and Antidiuresis in the Aged. A. Surtshin, Department of Physiology and Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.

9:40 a.m. Effects of Age and Senile Psychoses upon Speed of Writing Digits and Words. James E. Birren and Jack Botwinick, Section on Gerontology, National Heart Institute, National Institutes of Health, Bethesda, Maryland, and Baltimore City Hospitals, Baltimore, Maryland.

10:00 a.m. Psychologic Effects of Estrogen Therapy in Post-Menopausal Women. Bettye M. Caldwell, Robert I. Watson, and William B. Kountz, Division of Gerontology and Department of Psychology, Washington University School of Medicine, St. Louis, Missouri.

10:20 a.m. The Renal Extraction of Pah in the Aged Individual. John H. Miller, Roger K. McDonald, and Nathan W. Shock, Section on Gerontology, National Heart Institute, National Institutes of Health, Bethesda, Maryland, and Baltimore City Hospitals, Baltimore, Maryland.

10:40 a.m. A Comparison of Cardiovascular Responses to Tilting and Standardized Exercise in Old and Young Males. Arthur H. Norris, Nathan W. Shock, and Marvin J. Yiengst, Section on Gerontology, National Heart Institute, National Institutes of Health, Bethesda, Maryland, and Baltimore City Hospitals, Baltimore, Maryland.

11:00 a.m. 1. Effect of Steroids on the Aging Skin. 2. The Effect of Prolonged Steroid Therapy on Creative Output of an Aged Artist. Joseph W. Goldzieher and Max A. Goldzieher, New York, New York.

11:25 a.m. Reestablishment of Body Function in the Aged. William B. Kountz, Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.

11:45 a.m. Responses of Aged Persons to Salt and Desoxycorticosterone Acetate Tolerance Test (Soffer). Thomas H. McGavack, Jacqueline Chevalley, Ann M. Sheaman, Jonas Weissberg, and I. J. Drekter, New York Medical College, New York, New York.

12:05 a.m. A Comparative Study of Senile Changes in the Salivary Glands of Man and of the Rat. Warren Andrew. Department of Anatomy, George Washington University, School of Medicine, Washington, D. C.

12:25 p.m. Cytochemical Studies of Age Pigments in Man and the Rat. Edgar P. Jayne, Department of Anatomy, George Washington University School of Medicine, Washington, D. C.

Afternoon Session

E. V. Cowdry, Chairman

2:00 p.m. Significance of Medial Age Changes in the Human Pulmonary Artery. A. I. Lansing, T. B. Rosenthal, and M. Alex, Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri.

2:20 p.m. Chemical Pathogenesis of Arteriosclerotic Lesions. T. B. Rosenthal, M. Alex, and A. I. Lansing, Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri.

2:40 p.m. A Chemical Basis for the Observed Regional Distribution of Atheromata in the Human Aorta. M. Alex, A. I. Lansing, and T. B. Rosenthal, Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri.

3:00 p.m. Renal Pathology in Senile Guinea Pigs. James B. Rogers, Department of Anatomy, University of Louisville School of Medicine, Louisville, Kentucky.

3:20 p.m. Studies on Aging Processes in the Endocrine Glands of the Guinea Pig. II. The Effect of Estrogen and Corpus Luteum Hormone on Mitotic Activity in the Thyroid, Parathyroid, and Adrenal Glands of Guinea Pigs of Various Ages. H. T. Blumenthal, Department of Pathology, St. Louis University School of Medicine and Laboratory of the Jewish Hospital, St. Louis, Missouri.

3:40 p.m. The Effect of Topical Estrogen Application on the Elastic Properties of the Skin of Elderly Men. Margaret Chieffi, Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.

4:00 p.m. Quantitative Measurements of the Elastic Properties of the Skin and Subcutaneous Tissue in Middle-Aged Individuals. John Esben Kirk, Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.

4:20 p.m. The Effect of Ingestion of Large Amounts of Water and Milk upon the Life Span of Albino Rats. Clive M. McCay, Gladys Sperling, F. E. Lovelace, L. L. Barnes, and Clifton A. H. Smith, Laboratory of Animal Nutrition, Cornell University, Ithaca, New York.

4:40 p.m. Pathologic Studies of Rats Fed Varying Amounts of Fluid Throughout Life. J. A. Saxton, Jr., Gladys A. Sperling, Leroy L. Barnes, and C. M. McCay, Snodgras Laboratory of Pathology, St. Louis City Hospital, St. Louis, Missouri, and Laboratory of Animal Nutrition, Cornell University, Ithaca, New York.

5:00 p.m. Effect of Progesterone Administration on Old Men. P. From Hansen. Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.

5:20 p.m. Advances in the Treatment of Parkinsonism. Joseph C. Edwards, Emily Mueller, Masao Ohmoto, Gus Furla, and Sedgwick Mead, Division of Gerontology, Department of Internal Medicine, and the Division of Physical Medicine, Washington University School of Medicine, St. Louis, Missouri. To be presented in full at the meeting of the Southern Medical Association, Section on Medicine.

Program Committee

Robert J. Havighurst
A. I. Lansing
Ephraim Shorr
Edward J. Stieglitz
Clive M. McCay (Chairman)

Committee on Local Arrangements

John Esben Kirk
A. I. Lansing
William B. Kountz (Chairman)

Abstracts of Papers to Be Presented at the Third Annual Meeting of Gerontological Society, Inc.

COLLEGE PROFESSORS IN RETIREMENT. ELON H. MOORE. *Department of Sociology, University of Oregon, Eugene, Oregon.*

Analyses of the records of retirement experience of some 360 retired professors, made possible through the cooperation of the TIAA, gives us information on the adjustments to retirement experience for this occupational group. Such items as their degrees of satisfaction and dissatisfaction, their problems of income, and their employment or attempted employment in retirement years receive attention. The group who move from their home community is compared with those who remain in the location of their last assignment.

The relation of marital factors, children, and grandchildren to happiness in the retirement period reveals no marked correlation between happiness and the presence or absence of children. Further, widowers who lost their mates some years prior to retirement seem to fare quite as well as those whose mates survive. However, those who experience loss of mate after retirement reveal distinctly lower satisfaction with their lot.

A revealing comparison of the "happy" and "unhappy" retirants is found in their suggestions to others approaching retirement. The suggestions of the former are largely in agreement with their own experience whereas the suggestions of the discontended are quite in contrast with what they themselves experienced. Special analysis is made of the most dissatisfied retirants.

It is quite impossible to separate the adjustments and reactions peculiar to retirement from those which attend the processes of aging irrespective of retirement.

The selection of the sample from which this study is drawn may raise the question as to whether it is truly representative of the total body of retired professors. On the other hand there is every reason to believe that the analyses reveal the range of reactions and attitudes to retirement as well as indicate the bases of satisfaction or dissatisfaction in retirement experience.

COUNSELING AND GUIDANCE SERVICES FOR THE AGED. RUTH LAVERTY. *Peabody Home for Aged Women, New York, New York.*

Many applicants for Old Age Homes state that their need is not for institutional care but for help in the solution of their particular difficulties. They are in reasonably good health, mentally alert, well oriented, and articulate in the expression of their needs and should ordinarily be functionally capable of self help if the proper resources are made known to them. The major problems presented, it was found, related to the desire for financial assistance or employment, more adequate or congenial living quarters, recreational or diversional outlets, and the opportunity to make new friends and to fears about living alone, future illness, and strained family relationships.

When appropriate referrals were made, on the basis of the stated request, to other social agencies better equipped to handle such problems, it was noted that relatively few utilized the suggestions made. Further investigation revealed that these same people had made similar requests elsewhere with no evidence of having profited by the plan evolved with them, which they seemingly accepted at the time as the solution to their particular situations. A significant percentage repeated the identical request at periodic intervals with little or no carry-over gain from previous discussions. Some did not even remember having discussed these problems before, although their memories were not defective in other areas. Their situations in the meantime remained relatively unchanged, with no indication of their having any move to relieve the difficulty about which they consistently expressed concern. This repetitive pattern pointed to the need for further inquiry into the factors which seem to impede action.

Consequently, Peabody Home for Aged Women set up a counseling and guidance service on an experimental basis. The group of elderly women who presented such problems to this agency during the period of a year were studied intensively from a casework point of view. The paper will deal with the findings of this study.

A COMPARISON OF FACTORS IN THE PERSONAL ADJUSTMENT OF OLD PEOPLE IN PROTESTANT CHURCH HOMES FOR THE AGED AND OF OLD PEOPLE LIVING IN PUBLIC INSTITUTIONS. JU-SHU PAN. *University of Chicago, Chicago, Illinois.*

The purpose of this study was to indicate, as far as feasible, the influence of institutionalization upon personal adjustment in old age. The study investigated the factors affecting personal adjustment of aged persons living in private institutions as compared with aged persons living in public institutions in order to reveal those factors which are related to successful adjustment in old age as defined by attitude scores on the schedule, Your Activities and Attitudes, designed by R. S. Cavan, R. J. Havighurst, and E. W. Burgess. This schedule contains sections on back-

ground, questions on activities, and an Attitudes Inventory relating to adjustment in old age.

Five hundred and ninety-seven institutionalized women 65 years of age or older living in 68 Protestant church homes for the aged were selected for the present study. These cases were compared with a sample of 56 old women living in 2 public institutions in the south. The latter study was conducted by Blanche C. Junkin. All comparisons were made on the basis of scores on the Activities and Attitudes Schedule.

In comparison with the 56 women living in public institutions the Protestant home residents showed better familial relationships, more hobbies, and deeper religious convictions. This last item may be the result of sample selection.

Median attitude scores of the present sample exceeded those of the Junkin sample in attitude toward health, family, friends, leisure, employment, usefulness, and happiness. Those institutionalized in Protestant homes may be considered definitely better adjusted than the sample from public institutions.

Because of sample selection and bias introduced by the problem of nonresponse in studies of old age, the observations of the present study must remain tentative. They suggest, however, that residents of the religious homes have a better adjustment than residents of publicly operated homes.

SOCIAL ROLES AND THE PREVENTION OF SENILITY. Ruth Albrecht. *Committee on Human Development, University of Chicago, Chicago, Illinois.*

The problem was to find how the various factors of social role-activities influenced good adjustment and were related to youthful personality in people over 65 years. The study included family relationships, group and community activities, individual and peer participation, as well as economic, prestige, and status factors.

By the proportional stratified sampling method 100 subjects were selected representing a Midwestern community population of people over 65 according to age, marital status, sex, and social class positions.

Information was obtained by interview, a schedule, and membership lists. Three measuring instruments were used:

1. A Role-Activity Scale was constructed to rate activity on a 10 point scale within 15 different areas.
2. A Personality Register was devised to rate elderly people on the characteristics generally ascribed to aging: Cantankerousness, impulsiveness, interest in the past, mental lapse, unhappiness, and withdrawal.
3. The Cavan Scale of Personal Adjustment Ratings for Later Maturity was used to rate the degree of integration into social life and the attitudes significant for adjustment in these years.

Significant differences were found in certain role-activities between groups defined on the basis of marital status, age, and social class:

1. Married people were more active in social areas.
2. The social status position influenced role-activity in old age.
3. Chronologic age showed less discrimination than other factors.

Positive correlation coefficients were found between measurements of personal adjustment and the degree of activity in various role-areas. Individual patterns of activity were found which differ little from those of middle-age.

THE MEANING OF WORK IN RELATION TO RETIREMENT POLICY. Robert J. Havighurst. *Committee on Human Development, University of Chicago, Chicago, Illinois.*

Retirement from one's life-work is much more than an economic problem. Many people who have ample financial resources become seriously maladjusted because of retirement. This fact suggests that it may be useful to examine the meaning of work for various people and to use the results of this examination in the formation of policies of retirement and in the preparation of people for retirement.

The writer first formulated a number of hypotheses about the meaning of work on the basis of interviews with a variety of old people. Work may have one or more of the following meanings for people:

1. Pleasure from working with people.
2. Self respect.
3. Respect from others.
4. Means of livelihood.
5. New experience.
6. Chance for creativeness.
7. Means of preventing boredom.
8. Unpleasant necessity.

This paper reports the results of preliminary studies on the meaning of work to people of middle-age and later maturity in the following groups: teachers, skilled workers, white-collar workers, YMCA secretaries, and a cross-sectional group of men over 65 from a small city.

PSYCHIATRIC AND GROUP THERAPY AND CASEWORK IN SUPPORT OF DIABETIC TREATMENT. Julius Weil. *The Montefiore Home, Cleveland Heights, Ohio.*

With the progress in geriatrics in the past ten years, nutrition in general, and the diabetic diet in particular, has become a focal point in the care of older people. As soon as Mt. Sinai Hospital reopened its Diabetic Clinic after the war, those residents of the Montefiore Home who had diabetes were in-

cluded in the weekly check-up. A part-time dietitian was employed to supervise the preparation and administration of the three types of diabetic diets in the Home.

The value of diet in the treatment of diabetes was explained to the 16 patients in order to secure their cooperation in adhering to the particular diet prescribed. Reviewing the situation ten months later, it was observed that only one of the patients showed progress.

It was then decided that the psychiatrist hold weekly group-therapy meetings with the diabetic patients, that the caseworker intensify her interpretation, and that meetings be held with the families of the patients to demonstrate the adverse effects produced in supplying their relatives with food not on the diet.

A survey three years after the institution of the program revealed that 6 out of the 16 diabetic patients had participated regularly in the group meetings and the diet of another 6 could be controlled in the Montefiore Home. As a result of the efforts it was found possible to discontinue insulin treatment in 5 of the patients, and 3 of these were allowed a free diet. It was concluded that the educational program for the patients and their families brought results in the treatment of diabetes.

A COMPARISON OF AGING PROCESSES IN THE PULMONARY ARTERY AND AORTA. H. T. Blumental, Fred P. Handler, Jack Zuckner and S. H. Gray. *Department of Pathology, St. Louis University, School of Medicine, Laboratory of the Jewish Hospital, and Snodgras Laboratory, City Hospital, St. Louis, Missouri.*

A comparison by decades of aging processes in the thoracic and abdominal portions of the aorta with those in the main pulmonary artery has been carried out. A basic anatomic difference between the character and arrangement of elastic fibers in these two vessels has been noted, as well as differences in their age-changes. The latter are related to differences in the intensity and rate of calcification of the media. The abdominal aorta shows the most severe changes and the pulmonary the least; the thoracic portion of the aorta shows a progression of intermediate severity. Chemical data consisting of the percentages of total ash and calcium ash are correlated with the morphologic observations.

DIURESIS AND ANTIDIURESIS IN THE AGED. A. Surtshin. *Department of Physiology and Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.*

The diuresis pattern in response to drinking, at one sitting, an amount of water equal to 2 per cent of the body weight was determined in 7 individuals ranging from 75 to 86 years of age. These individuals were clinically free from cardiac failure and from liver or renal disease other than nephrosclerosis. The diuresis pattern showed no significant difference from responses obtained in young healthy individuals.

In 4 females ranging from 70 to 86 years of age, a maintained diuresis was produced by ingestion of an initial amount of water (1 per cent of body weight) and subsequent amounts (0.15 per cent of body weight) every fifteen minutes. During such maintained diuresis, determination was made of the minimal amount of Pitressin injected intravenously, causing inhibition of the diuresis. The values obtained ranged from 2 to 4 milliunits. These values are similar to those determined for younger individuals ranging from 13 to 36 years of age and to those reported in the literature for young adults.

It seems that the water diuresis response of the aged is normal, without commitment as to whether the response to hemodilution is that of the posterior pituitary osmoreceptors or of the renal tubules. The sensitivity of the renal tubules to Pitressin (antidiuretic hormone) is of the same order as in younger individuals.

EFFECTS OF AGE AND SENILE PSYCHOSES UPON SPEED OF WRITING DIGITS AND WORDS. James E. Birren and Jack Botwinick. *National Heart Institute, National Institutes of Health, Bethesda, Maryland, and Section on Gerontology, Baltimore City Hospitals, Baltimore, Maryland.*

Measurements of the speed of writing digits and words were made on 554 subjects between the ages of 16 and 89 years and on 35 patients institutionalized in mental hospitals for senile psychosis or cerebral arteriosclerosis with psychosis. All subjects had four or more years of schooling and had English as their native language. The subjects were required to write digits and short words as quickly as they could for a maximum of two minutes each. The estimated reliability of the two-minute tests of digit and word writing is above 0.90.

Large age differences were found for both speed of writing digits and words; the difference between subjects aged 16 to 20 and subjects 80 to 89 years was $-4.9\,\sigma$ for digits and $-5.8\,\sigma$ for words, or a decline of 70.7 and 66.5 per cent, respectively, in mean value. Correlation ratios, η, between age and speed of writing were 0.83 for digits and 0.87 for words.

Significantly lower speed of writing was observed in the patients with senile psychoses when they were compared with control subjects of the same chronologic age. Differences of 0.30 digits/second, or 37 per cent, and 5.9 words per two minutes, or 27 per cent, were obtained between the control and patient populations (both P valves $<$ 1 per cent).

In view of the present results the measurement of speed of writing seems to be a valuable adjunct to the psychologic evaluation of the individual elderly person.

PSYCHOLOGIC EFFECTS OF ESTROGEN THERAPY IN POSTMENOPAUSAL WOMEN. BETTYE M. CALDWELL, ROBERT I. WATSON, AND WILLIAM B. KOUNTZ. *Division of Gerontology, and Department of Neuropsychiatry, Washington University School of Medicine, St. Louis, Missouri.*

With the continued advance in the scientific study of the aging process, endocrinologic factors loom large as influencing to some degree the rate of approach to senescence. Exploratory studies involving the use of estrogens with aged females have shown, in addition to certain physical improvements, many psychologic modifications which are in themselves desirable treatment goals. Objective evidence of these psychologic changes is lacking, however, and it is the purpose of this study to investigate the effects of this type of therapy in order to objectify such changes if they do exist, or at least to delimit more conclusively the areas of effectiveness of the therapy in the event no psychologic benefits can be detected.

Thirty women (mean age 75.5) have been isolated over a period of several months in one ward of a City Home for the Aged. Half the patients received various dosages of estrogen followed by estrogen withdrawal to induce bleeding, with the bleeding controlled in such a way as to simulate the menstrual cycle, while the other half received placebos. No other differential treatment has been accorded the 2 groups.

Prior to the introduction of the estrogen therapy, and again after six months of the therapy, a battery of psychologic tests was administered. The tests were chosen to sample such functions as general intelligence, memory, energy level, degree of optimism or pessimism, initiative, placticity of thought processes, and predominant mental conflicts. In order to minimize contamination of the results the psychologist did not learn the identity of the 2 groups until after the second battery had been administered and scored. Statistical evaluation of the data followed.

It is the purpose of this paper to discuss the differential findings in the 2 groups, together with certain implications for future research which present themselves as a result of this investigation.

THE RENAL EXTRACTION OF PAH IN THE AGED INDIVIDUAL. JOHN H. MILLER, ROGER K. MCDONALD, AND NATHAN W. SHOCK. *National Heart Institute, National Institutes of Health, Bethesda, Maryland, and Section on Gerontology, Baltimore City Hospitals, Baltimore, Maryland.*

Although the validity of diodrast and p-aminohippurate clearance as a measure of renal plasma flow in the normal young subject has been established, the demonstration of a decrease in the maximal rate of diodrast excretion with age has raised doubt as to the validity of the use of PAH or diodrast clearance as a measure of renal plasma flow in the old person.

In the present study, renal vein catheterization was performed in 27 subjects who ranged in age from 23 to 75 years, and the renal extraction of PAH at low plasma levels was determined. All subjects selected were free of clinical evidence of cardiovascular and renal disease.

The fraction of PAH extracted from the plasma by the kidney ranged from 0.865 to 0.968 with a mean of $0.913 \pm .025$ for the entire group of subjects. There was no significant correlation between renal extraction and either age or PAH clearance.

It is concluded that the clearance of PAH is a valid measure of renal plasma flow in the old as well as the young and that the previously observed decreases in diodrast and PAH clearance in older individuals represent an actual decrease in renal plasma flow.

A COMPARISON OF CARDIOVASCULAR RESPONSES TO TILTING AND STANDARDIZED EXERCISE IN OLD AND YOUNG MALES. ARTHUR H. NORRIS, NATHAN W. SHOCK AND MARVIN J. YIENGST. *National Heart Institute, National Institutes of Health, Bethesda, Maryland, and Section on Gerontology, Baltimore City Hospitals, Baltimore, Maryland.*

Blood pressure and pulse rate responses to tilting to 45° and 90° and to a standardized (rate and amount of work) exercise step test were measured in 140 males between the ages of 20 and 90 years. The elderly subjects were an unselected sample of ambulatory residents in the Baltimore City Hospitals Infirmary Division (Old People's Home). The young and middle-aged groups included hospital employees and staff members.

Pulse rates were recorded continuously with a microphone pick-up. Blood pressures were recorded by the auscultatory method at 30-second intervals beginning 15 seconds after each change in position. After fifteen minutes of rest in the horizontal position, during which measurements were made, the subject was tilted to 45° for ten minutes, after which he was returned to the horizontal position for ten minutes. He was then tilted to the vertical position for six minutes, after which he was seated for six minutes. The subject then walked over a pair of steps (18" total height) at a specified rate. All subjects performed 222 kg.m. work in 1½ minutes (S.D. = 16 kg.m.). Average values were computed for each measurement according to age.

After tilting to 45° the old subjects showed a greater fall in systolic pressure and a smaller rise in

pulse rate than did the young. Similar differences were found in the pulse rate response to the vertical position. However the blood pressure response was both qualitatively and quantitatively different. The old subjects responded to the standard exercise with greater increases in both blood pressure and pulse rate than did the young. Although the heart in the aged subjects showed a greater increase in rate following the metabolic demand of exercise than did the young, the response to changes in posture was less. Apparently the mechanisms involved in the regulation of pulse rate are less sensitive in the old than in the young.

EFFECT OF STEROIDS ON THE AGING SKIN. Joseph W. Goldzieher and Max A. Goldzieher. *New York, New York.*

Complete studies have been carried out on 30 controls and 34 aged individuals in an attempt to correlate the case history as well as physical, medical, metabolic, and endocrine status with the age and appearance of the skin.

The epidermis was studied by means of multiple biopsies on which histochemical determinations were carried out and by spectrophotometric reflectance analysis, which was correlated with the histologic observations. Alpha estradiol, beta estradiol, estrone, testosterone, methylandrostenediol, pregnenolone, and calciferol in various concentrations were applied to the skin twice daily in a volatile solvent over periods ranging from 10 days to 140 days. Nearly 500 serial biopsies were made at 10 to 15 day intervals.

The effect of these various steroids on epithelial regeneration will be discussed and the histochemical findings in the epithelial and subepithelial tissue correlated with the spectrophotometric technique.

THE EFFECT OF PROLONGED STEROID THERAPY ON CREATIVE OUTPUT OF AN AGED ARTIST. Joseph W. Goldzieher and Max A. Goldzieher, *New York, New York.*

An aged painter has been under our observation and treatment for the past six and a half years, during which time he has been on intermittent therapy with varied doses of steroids. Definite correlations have been noted between the qualitative and quantitative aspects of his creative output and the physical response to his treatment. Reproductions of his paintings (Kodachromes) will be used to demonstrate the correlation.

REESTABLISHMENT OF BODY FUNCTION IN THE AGED. William B. Kountz. *Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.*

Under controlled circumstances in which individuals have been carefully worked up, attempts have been made to reestablish body function, particularly the cycle of menstruation in the aged female, the ability of the body to utilize carbohydrate and protein, and the restoration of oxygen consumption.

In the study older people from 65 to 85 years of age were used. It has been found that the response of the older person to the proper substitution therapy in many instances may be returned to that of a younger person and in every respect resemble what is considered to be normal. This is particularly true in a case of administration of the sex hormones and in the feeding studies with protein and carbohydrate metabolism.

Charts and photographs will be presented which demonstrate improved specific tissue function and improved body function and demonstrate also that such forms of therapy will not lead to untowards disease processes if handled properly.

RESPONSES OF AGED PERSONS TO SALT AND DESOXYCORTICOSTERONE ACETATE TOLERANCE TEST (SOFFER). Thomas H. McGavack, Jacqueline Chevalley, Ann M. Shearman, Jonas Weissberg, and I. J. Drekter. *New York Medical College, New York, New York.*

From the study of approximately 100 complete tests with salt and salt and desoxycorticosterone acetate, effort will be made to appraise the responses of the pituitary adrenal system in older people. In connection with these studies, aged persons with obvious renal dysfunction have not been included. Some of the subjects may be suffering from diseases commonly falling within the group associated with Selye's adaptation syndrome. Our major objective will be to present differences and similarities in the reaction in people above 50 as compared with those in younger age groups. The simultaneous behavior of urinary 17-ketosteroids, uric acid, creatinine, potassium, sodium, chloride, and rate of urinary flow will be made a basis for evaluating adrenal activity.

A COMPARATIVE STUDY OF SENILE CHANGES IN THE SALIVARY GLANDS OF MAN AND OF THE RAT. Warren Andrew. *Department of Anatomy, George Washington University School of Medicine, Washington, D. C.*

Specimens of human salivary glands, both parotid and submandibular, have been obtained, chiefly from surgical cases.

In the human parotid gland, as in the rat, the amount of fatty degeneration in old age is very great, and frequently seems to lead to a destruction of as much as 50 per cent of the original glandular tissue. The pattern of degeneration is similar in that "islands" of relatively intact tissue, irregular in out-

line, remain within the adipose tissue both in rat and man.

In the submandibular gland of man fatty degeneration is much less marked than in the parotid gland, but it is present to a greater degree than in the rat submandibular gland.

The existence of oncocytes (large, aberrant epithelial cells, originally first described by Hamperl in examination of human salivary glands, and confirmed by me for the rat) has been difficult to affirm in most of the human parotid specimens. On the other hand, some of the senile specimens definitely do show such cells, characterized by the large size of the cell body, conspicuously reticulated cytoplasm, and aberrant nuclei.

Attention has been given to a possible mechanism of fatty degeneration, not hitherto described, and also to the intimate association of epithelial and lymphoid tissue in these human salivary glands where intraglandular lymph nodes occur.

CYTOCHEMICAL STUDIES OF AGE PIGMENTS IN MAN AND THE RAT. EDGAR P. JAYNE. *Department of Anatomy, George Washington University School of Medicine, Washington, D. C.*

During the second decade of life a golden brown pigment begins to accumulate at the poles of the cardiac muscle fibers. Although this acid-fast pigment is insoluble in fat solvents, acids, and alkalis, the results of cytochemical tests indicate that it is an unsaturated lipoid which is possibly bound to a higher molecular weight protein. Results of attempts to correlate the amount of pigment occurring in the cardiac muscle with age indicate that, in general, pigmentation increases with age with respect to both the number of cells affected and the concentration per cell.

The mitochondria of the zona reticularis and zona fasciculata of the rat adrenal seem to be undergoing degenerative changes with age, resulting in the formation of intracellular pigment granules. These pigment-containing cells eventually break down leaving an extracellular conglomeration of pigment.

SIGNIFICANCE OF MEDIAL AGE CHANGES IN THE HUMAN PULMONARY ARTERY. A. I. LANSING, T. B. ROSENTHAL, AND M. ALEX. *Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri.*

This laboratory has stressed the view that arteriosclerosis is a problem of aging. Our observations indicate that calcification of medial elastic tissue predisposes both elastic and muscular arteries to form atheromata. Any concept of arteriosclerosis must account for the circumscribed distribution of arteriosclerotic lesions. Why do atheromata form in some vessels and not in others? Why, as in the aorta, do atheromata appear more frequently in the abdominal than in the thoracic portion?

The pulmonary artery is particularly important since it serves as a natural control for observations on the aorta; like the aorta it is an elastic artery having its origin close to the heart, but differs sharply from the former in that it is uncommon to find atheromata in the pulmonary artery. If the calcification of medial elastic tissue as demonstrated in the aorta is requisite to intimal plaque formation, then the senile pulmonary artery should be relatively free of this elastic tissue age change.

Data are presented which indicate that the calcium content of elastin of the pulmonary artery increases very slowly with age in contrast to the aorta which calcifies very rapidly with age. It is suggested that the infrequent occurence of pulmonary atheromata is dependent upon the low rate of calcification of the medical elastic elements.

CHEMICAL PATHOGENESIS OF ARTERIOSCLEROTIC LESIONS. T. B. ROSENTHAL, M. ALEX, AND A. I. LANSING, *Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri.*

The object of this investigation was to assay quantitatively the chemical constituents which are generally agreed to be the main features of the arteriosclerotic lesion. These are infiltration by cholesterol and calcium together with fibrous tissue proliferation of the intima. In addition our previous work has directed attention to calcification of medial elastic tissue as a predisposing factor in the origin of intimal plaques.

We concluded: (1) That in the absence of any gross or microscopic intimal changes there is a progressive rise with age in the calcium content of medial elastic fibers (from essentially zero to about 10 per cent). This chemical alteration of elastic tissue may be regarded as an inevitable consequence of aging. (2) That in plaques of comparable severity there are analytic chemical differences depending on the age of the individual. (3) That in the development of a plaque the accummulation of calcium in the underlying media precedes the infiltration of cholesterol to the overlying intima.

A CHEMICAL BASIS FOR THE OBSERVED REGIONAL DISTRIBUTION OF ATHEROMATA IN THE HUMAN AORTA. M. ALEX, A. I. LANSING, AND T. B. ROSENTHAL. *Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri.*

It is well known that atheromata usually occur more frequently and with greater severity in the abdominal than in the thoracic portions of the aorta;

also that there are anterior-posterior differences in severity and incidence.

Single aortas from a group of middle-aged individuals were divided into 6 parts by longitudinal and transverse cuts. We thus obtained the following areas: anterior and posterior thoracic, anterior and posterior upper abdominal, and anterior and posterior lower abdominal. From these areas the intimas and medias were separated and individually analyzed for calcium and cholesterol.

In those regions capable of showing a high frequency and marked severity of atheromata we consistently found an elevated medial elastic tissue calcification. On the other hand, intimal cholesterol levels were not as consistent. These measurements reinforce our view that calcification of medial elastic tissue is a primary predisposing factor in the genesis of an intimal plaque.

RENAL PATHOLOGY IN SENILE GUINEA PIGS. JAMES B. ROGERS. *Department of Anatomy, University of Louisville School of Medicine, Louisville, Kentucky.*

This is a report on the gross and microscopic pathologic conditions found in approximately 100 postmortem studies of the kidneys of senile guinea pigs.

Animals which have survived 1095 days or longer are considered senile because of the sharp decrease in reproductive activity at the end of the third year of life. Most of these senile animals were sacrificed while in fair physical condition and were perfused immediately. Animals found dead in their cages are also reported. In this latter group there were varied anatomic causes of death, such as acute intestinal obstruction, pericardial hemorrhage, cerebral hemorrhage, and peritonitis. There were also many deaths without demonstrable cause.

Polycystic kidneys and gross hemorrhage into the kidney substance were found grossly. Fatty infiltration of the proximal convoluted tubules was a common microscopic finding.

STUDIES ON AGING PROCESSES IN THE ENDOCRINE GLANDS OF THE GUINEA PIG. II. THE EFFECT OF ESTROGEN AND LUTEUM HORMONE ON MITOTIC ACTIVITY IN THE THYROID, PARATHYROID, AND ADRENAL GLANDS OF GUINEA PIGS OF VARIOUS AGES. H. T. BLUMENTHAL. *Department of Pathology, St. Louis University, School of Medicine, and Laboratory of the Jewish Hospital, St. Louis, Missouri.*

In a previous report we demonstrated the curves of diminution in mitotic activity with age in guinea pigs of both sexes. The present investigations deal with the ability of the ovarian hormones to modify these curves. Contrary to certain other reports, progesterone stimulates mitotic activity in these endocrine glands, particularly in the adrenal cortex, but the ability of the glands to respond to this stimulus diminishes with advancing age. Estrogen is a less potent stimulus than progesterone and may act as a mitotic inhibitor in certain instances.

In general, the conclusion may be drawn that the response of these glands is probably more dependent upon certain inherent age changes than upon the level of circulating hormone.

THE EFFECT OF TOPICAL ESTROGEN APPLICATION ON THE ELASTIC PROPERTIES OF THE SKIN OF ELDERLY MEN. MARGARET CHIEFFI. *Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.*

In a previous study it was found that local application of estrogen in oil improved the elastic properties of the skin of elderly women. The local application of testosterone in oil to the skin of men did not produce any change. The present study was undertaken to determine whether or not the topical application of estrogen to the skin of elderly men would result in improvement of the elastic properties.

One milligram of estradiol benzoate in peanut oil was applied three times weekly to a 40 square centimeter area of the skin in 12 elderly men over a period of two months. Quantitative measurements of the elasticity of the skin and subcutaneous tissue were performed before and during the treatment using the method described by Kirk and Kvorning. The results of these measurements will be reported.

QUANTITATIVE MEASUREMENTS OF THE ELASTIC PROPERTIES OF THE SKIN AND SUBCUTANEOUS TISSUE IN MIDDLE-AGED INDIVIDUALS. JOHN ESBEN KIRK. *Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.*

In a previous study a comparison was made between the elastic properties of the skin and subcutaneous tissue in a group of young and old individuals, using a modification of Schade's elastometer, and a sizable difference, especially in the degree of resilience, was noted between the young and old subjects. In the present study a group of men and women between the ages of 25 and 59 years have been subjected to similar measurements with the purpose of determining the age of onset of the impaired elastic qualities.

The results of these investigations will be reported.

THE EFFECT OF INGESTION OF LARGE AMOUNTS OF WATER AND MILK UPON THE LIFE SPAN OF ALBINO RATS. CLIVE M. MCCAY, GLADYS SPERLING, F. E. LOVELACE, L. L.

BARNES, AND CLIFTON A. H. SMITH. *Laboratory of Animal Nutrition, Cornell University, Ithaca, N. Y.*

Two hundred and forty rats were distributed into 4 groups of 60 each with the distribution based upon litter mates and sex. Each group was fed the experimental diets from the time of weaning. One group was fed only fresh, pasteurized cow's milk from the Cornell dairy herd. This milk was supplemented with 4 trace elements, namely Mn,Cu,Fe, and I plus 8 drops of cod liver oil weekly. The other 3 groups were fed a complete ration of natural foods, known to be satisfactory for the growth and reproduction of dogs and rats.

One of these 3 groups served as a control and received only water to drink; another was given 10 per cent sucrose solution to drink instead of water in order to insure a large ingestion of water; the third group was given coffee as made for human consumption instead of water. The diet of the group given only water was supplemented with an amount of sugar so that the amount ingested was equal to that drunk by the group of rats given the 10 per cent sucrose solution.

These 4 groups of rats were kept throughout life in an air-conditioned room. The 4 groups were compared in relation to mortality rates, diseases that developed, amounts of fluid ingested, density of bones, calcification of soft tissues, and condition of teeth at the end of life.

PATHOLOGIC STUDIES OF RATS FED VARYING AMOUNTS OF FLUID THROUGHOUT LIFE. J. A. SAXTON, JR., GLADYS A. SPERLING, LEROY L. BARNES, AND C. M. MCCAY. *Snodgras Laboratory of Pathology, St. Louis City Hospital, St. Louis, Missouri, Laboratory of Animal Nutrition, Cornell University, Ithaca, New York.*

Rats were studied after they had been fed 4 sources of fluid from weaning until natural death in old age. Two groups had ingested large amounts of fluid daily in the form of milk and 10 per cent sucrose solution while 2 groups had ingested moderate amounts of fluid in the form of water and coffee made as a beverage.

EFFECT OF PROGESTERONE ADMINISTRATION ON OLD MEN. P. FROM HANSEN. *Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.*

Progesterone was administered intramuscularly to 16 old men in weekly doses of 100 mg. The effects upon the acid prostatic phosphatase, the beard growth, and the skin elasticity were determined.

ADVANCES IN THE TREATMENT OF PARKINSONISM. JOSEPH C. EDWARDS, EMILY MUELLER, MASAO OHMOTO, GUS FURLA, AND SEDGWICK MEAD. *Division of Gerontology, Department of Internal Medicine, and Division of Physical Medicine, Washington University School of Medicine, St. Louis, Missouri.*

A clinical study of the effects of several drugs was conducted on 22 patients with Parkinson's disease. These drugs included, among others, artane, benadryl, rabellon, perazil, di-hydro-beta erythroidine-hydrobromide in various combinations.

Each drug, groups of drugs, and placebos were studied for a period of one week. The effects of the medicines were evaluated by the observations of physicians and nurses, the subjective feelings of the patients (their ability to feed themselves and walk and do selected exercises each week), and the use of 16 mm. motion pictures and electromyograms.

Ten patients had the arteriosclerotic type and 12 had the postencephalitic type of Parkinson's disease. The patients rated the effect of the drugs as poor, better, and best by the use of a point system. A physician rated the effect of the drugs on each patient, and the electromyograms were likewise rated for each drug.

Nine patients were greatly improved, 8 were somewhat better, and 5 were not improved. The best results were obtained in most cases by a combination of artane (2 to 5 mg.), benadryl (50 mg.), and one tablet of rabellon (hyoscine, atropine, scopolamine) three times daily after meals. Four patients were able to walk and to feed themselves for the first time in years. The effects of the various drugs and the results of the above tests and methods are described. The important help these drugs offer and the need for cautious and not abrupt withdrawal of them in any patient is discussed.

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FIRST INTERNATIONAL CONFERENCE OF GERONTOLOGY

This was held at the University of Liège, Liège, Belgium, July 10 to 12 inclusive, 1950, under the Presidency of Dr. L. Brull, Professor of Medicine and Dean of the School of Medicine. Ninety-six persons from fourteen countries attended. The proceedings will be published in Belgium.

The January issue of the Journal of Gerontology will describe this conference more fully, also the Primer Congreso Nacional de Geriatria, Barcelona, Spain, June 15 to 18, 1950, and Lord Nuffield's Conference on Gerontological Research, London, July 8, 1950.

The Second International Conference of Gerontology will be held in the Hotel Jefferson, St. Louis, Missouri, Sept. 9 to 14 inclusive, 1951, if the world situation permits, or as soon thereafter as is feasible. Information can be obtained from Dr. E. V. Cowdry, Washington University School of Medicine, St. Louis 10, Missouri.

BOOK REVIEWS

HEALTH EDUCATION

BIOLOGICAL FOUNDATIONS OF HEALTH EDUCATION, Proceedings of the Eastern States Health Education Conference, April 1-2, 1948, New York Academy of Medicine, Columbia University Press, New York, 1950, 169 pages, $2.50.

This book includes the texts of fourteen essays presented by scientists pre-eminent in the fields of nutrition, psychiatry, gerontology, and epidemiology at a conference on health education sponsored by the New York Academy of Medicine. An attempt has been made not only to summarize the important present day concepts in these fields but also to interpret facts so that they may be effectively utilized by health educators.

It is an important occasion whenever authorities from medical science meet with those from education to consider the major health problems. Accomplishments within the field of the health sciences have been great during recent decades but the full significance of these advances cannot be realized until they are made to work for the public welfare. Important advances in the guarding and maintaining of health must be interpreted to all segments of society in such a way that modes of living are changed and adapted to best health practices. As is repeatedly emphasized in this book, the health educator must evaluate his effectiveness by assessment of what the learner learns and not what the teacher teaches.

Chronic and degenerative disease is presented, as it should be, as the chief medical and health problem of the world today. A large part of the book is concerned with considerations pertinent to gerontology. Essays are included by Clive McCay on Gerontology and Nutrition, Edward J. Stieglitz on Orientation in Gerontology, Carlos Schaffenburg on The Growth and Aging Processes, and Antonio Ciocco on An Epidemiological Approach to Chronic Diseases through Family Studies.

Of particular interest to the reviewer was the significance given to the use of epidemiologic methods in the study of degenerative disease. Such methods have already defined the present community problem in this area. There is real reason to desire an extension along this avenue of investigation in a search for underlying sociologic and environmental factors which may influence the occurrence of the debilitating diseases of old age.

As is true of any book to which a number of authors have contributed, there is variation in style of presentation and effectiveness of writing. On the whole, however, there is a constancy of purpose and direction in these essays. Biological Foundations of Health Education is an excellent book for the health educator and should assist in giving substance and new techniques to programs in this field. The book should also be read with advantage by the physician who desires an evaluation of his role as health educator and agent working toward better community health—social responsibilities which are inseparable from and daily more significant in the practice of medicine.

R. E. SHANK

BIOGRAPHY OF A PSYCHOLOGIST

PSYCHOLOGIST UNRETIRED—The Life Pattern of Lillien J. Martin, Miriam Allen de Ford, Stanford University Press, Stanford, California, 1948, 127 pages, $3.00.

To students of old age the name of Lillien J. Martin has long been familiar as a pioneer student of the needs of the elderly. Since she died as recently as 1943, at the age of 92, many

of the readers of this Journal must have known her personally. The present volume is a biographic tribute and appreciation by an accomplished writer, who was ably assisted by Dr. Martin's many friends. The book is dedicated to the memory of Claire Moore de Gruchy, long the faithful co-worker of Lillien Martin.

The development of Miss Martin from her girlhood and early teaching experiences to her entry into Vassar as an undergraduate in 1880 at the age of twenty-five years is described in sufficient detail for us to understand her character in its formative period. Her adult life was divided into three distinct phases, a teacher of general science in high schools, a college teacher of psychology, and finally an applied psychologist.

Chapters six and seven, devoted to her years of study in Germany and her life as a faculty member at Stanford University, have been written by Dr. J. Harold Williams. Her difficulties in gaining admission to the lectures at Goettingen, her participation in student life, and her troubles in mastering German make interesting reading. The record of her achievements as an academic teacher and as a research worker is most impressive, as is also the listings of the many honors accorded her in professional circles, including an honorary Ph.D. from the University of Bonn.

In 1916 having attained the age of sixty-five years Lillien Martin was retired from her position at Stanford University, but she was far too energetic to be satisfied with doing nothing. She became a consulting psychologist and opened mental hygiene clinics in two San Francisco hospitals. From her interest in children grew her interest in their grandparents which later flowered in the famous Old Age Counselling Center, established in 1929.

This is a sympathetic and authoritative life of a great woman whose teachings and precepts are a vital part of our heritage. It is particularly valuable to those who have known only her last years without understanding how she achieved her eminence or realizing how numerous were her original contributions before ever turning to clarify the problems of old age.

F. D. ZEMAN

PSYCHIC CHANGES WITH AGE

SEELISCHE WANDLUNGEN BEIM ALTERNDEN MENSCHEN (Psychic Changes in Aging Individuals), A. L. Vischer, Benno Schwabe and Co., Basel, 1949, 216 pages, $3.50. American representative, A. J. Phiebig, Suite 906, 545 Fifth Avenue, New York 17.

Dr. A. L. Vischer, Director of the Municipal Home for the Aged in Basel, Switzerland, established his reputation as a wise clinician and a discerning student of old age with his first book, *Old Age, Its Compensations and Rewards (Das Alter als Schicksal und Erfüllung)*, published in London in 1947. The present work, as yet untranslated, enlarges and emphasizes the concepts previously set forth. The author's aim is to enlighten the younger generation and to prepare them for aging, as well as to offer stimulating guidance to the old themselves.

Vischer's method of procedure is unique in attempting the correlation of his clinical studies of the old with the observations of famous writers, such as Goethe, La Fontaine, de Maupassant, Fontane, Galsworthy, T. S. Eliot, Renan, and countless others. His familiarity with world literature is utilized in striking fashion to complement his objective findings. "The writer does not produce his works on the basis of theoretical concepts like the scientist, but as a sensitive participant in life. The artist may describe a single case in such a way that this case becomes not only significant in its own concrete unity, but also points toward a broad generalization . . . Galsworthy expresses in the *'Indian Summmer'* of the *Forsyte Saga* the actual reality of an old man in a way that cannot be accomplished analytically. The same is true of Maupassant's novel, *Fort*

Comme la Mort, which describes the inner experience of aging."

This employment of subjective observations on aging is so skillfully handled by Dr. Vischer that his book is replete with value for both the clinician and the layman. His contrasting of the mind in youth and age gives full emphasis to the changing sense of values that comes with the years. Couched in literary and philosophic terms, it is a contribution to the understanding of the human mind without recourse to the jargon of modern psychiatry. The references direct attention to many sources that have never before been tapped by students of this subject. The reviewer is hopeful that somewhere a devoted translator is already at work putting this unusual book into English.

F. D. ZEMAN

BOOKS RECEIVED

Books received since May 1, 1950, are acknowledged in the following list. In so far as space and time permit, some will be selected for review in a later issue, but it is unlikely that all will be reviewed.

Biological Foundations of Health Education, Proceedings of the Eastern States Health Education Conference, April 1-2, 1948, New York Academy of Medicine, Columbia University Press, New York, 1950, 169 pages, $2.50 (reviewed in this issue, page 392).

Clubs for the Golden Age, A Study of Recreational Activities for Ohio's Older Citizens, The Ohio Citizens' Council for Health and Welfare, Columbus, Ohio, 64 pages, paper bound, $1.00.

Geriatric Nursing, by Kathleen Newton, C. V. Mosby Company, St. Louis, Missouri, 1950, 420 pages, $4.50.

Human Milk, Wartime Studies of Certain Vitamins and Other Constituents, by S. K. Kon and E. H. Mawson, Medical Research Council Special Report Series No. 269, London, 1950, 188 pages, paper bound, 4 shillings. Copies may be ordered from the British Information Services, 30 Rockefeller Plaza, New York 20, New York.

Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Bulletin of the World Health Organization Supplement 1, Columbia University Press, New York, $6.00 (two volumes). Volume 1, 1948, 376 pages; Volume 2 (Alphabetical Index), 1949, 524 pages.

Need for Emotional Adjustments in the Elderly, by L. Cosin, National Council of Social Service, Inc., London, 1950, 20 pages, one shilling.

Old Age, Some Practical Points in Geriatrics and Gerontology, by Trevor H. Howell, H. K. Lewis & Co., Ltd., London, 1950, 108 pages, paper bound, 10 shillings, 6 pence.

Physiology of Tissues and Organs, by Douglas H. R. Lee, Charles C Thomas, Publisher, Springfield, Illinois, 1950, 159 pages, $4.00.

Researches on the Measurement of Human Performance, by N. H. Mackworth, Medical Research Council Special Report Series No. 268, London, 1950, 156 pages, paper bound, 4 shillings. Copies may be ordered from the British Information Services, 30 Rockefeller Plaza, New York 20, New York.

Resources of Old-Age and Survivors Insurance Beneficiaries in Philadelphia and Baltimore, 1949, Federal Security Agency, Social Security Administration, Bureau of Old-Age and Survivors Insurance, Division of Program Analysis, Washington, D. C., May, 1950, 33 pages.

Selected Studies on Arteriosclerosis, by Rudolf Altschul, Charles C Thomas, Publisher, Springfield, Illinois, 1950, 182 pages, $5.50.

INDEX TO CURRENT PERIODICAL LITERATURE

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The subject categories are those used in *A Bibliography of Gerontology and Geriatrics* by Nathan W. Shock to be published by Stanford University Press, Stanford, California. Only major headings will be used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available abstract references are given (*B.A.* indicates *Biological Abstracts; P.A.* indicates *Psychological Abstracts*). Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the years 1900-1933,* 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints.

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976. Bourlière, F.: Biologie de la sénescence. *In: Le Problème du Vieillissement,* Paris, 1948, Sect. III, pp. 6-53.
977. Howell, T. H.: *Old age; some practical points in geriatrics and gerontology.* H. K. Lewis & Co. Ltd., London, 2nd Ed., 1950, vii, 108 pp.
978. Howell, T. H.: Teaching and research in problems of old age. *Med. Pr., 223:* 39-41, 1950.
979. Jacobsen, E.: *Alderens problem.* H. Hirschsprungs Forlag, Kbh., 1947, 218 pp.
980. Jacobsen, E.: *Åldrandets problem.* Tidens Förlag, Stockholm, 1949, 192 pp.
981. Klumpp, T. G.: Old age. *N. Y. St. J. Med., 49:* 1929-1933, 1949.
982. Moore, R. A.: The medical approach to the problems of aging. *J. Geront., 4:* 90-94, 1949.
983. Robinson, H. G.: Grandmothers are guinea pigs. *J. Geront., 4:* 245-247, 1949.
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985. Thewlis, M. W.: What is "normal senility"? *Geriatrics, 5:* 44-45, 1950.
986. Tuohy, E. L.: The terms "geriatrics" and "gerontology." *Geriatrics, 5:* 45, 1950.
987. Vischer, A. L.: Aufgaben und Begrenzung der Altersforschung. *Bull. schweiz. Acad. med. Wiss., 5:* (4), 290-301, 1949.

See also No. 1039.

BIOLOGY OF AGING

I. CELLULAR BIOLOGY AND PHYSIOLOGY (includes plants)

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IV. LONGEVITY

989. Dublin, L. I.: Our aging population. *Comm. & Financ. Chron., 169:* 1734-1735, 1949.
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991. Gross, M. Z.: Why fat people die sooner. *Hygeia, Chicago, 27:* 96-97; 130-131, 1949.
992. Hedback, A. E.: How long will your heredity clock tick? *Geriatrics, 4:* 196, 1949.
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longevity expected. *Statist. Bull. Metrop. Life Insur. Co., 29:* 5-8, Nov. 1948.

995. Sherman, H. C., H. L. Campbell, and M. S. Ragan: Analytical and experimental study of the effects of increased protein with liberal calcium and riboflavin intakes: Complete life cycle. *J. Nutrit., 37:* 317-327, 1949.

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IV-C. Longevity: *Comparative Physiology*

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IV-H. Longevity: *Mortality Rates*

1005. Berkson, J.: Calculation of survival rates for cancer. *Proc. Mayo Clin., 25:* 270-286, 1950.

1006. Boverat, F.: Comparison de la mortalité urbaine et de la mortalité rurale aux Etats-Unis. *In: Le Problème du Vieillissement,* Paris, 1948, Sect. III, pp. 89-92.

1007. Bransby, E. R., and D. V. Lindley: Mortality during the 1st World War and during and after the 2nd World War. *Mon. Bull. Min. Hlth. Lab. Serv., Lond., 9:* 2-12, 1950.

1008. Jenkins, W. A., and E. A. Lew: A new mortality basis for annuities. *Soc. Actuar., 1:* 369-466, Nov. 1949.

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V. Metabolism

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VI. Nutrition

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IX. Rejuvenation

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ORGAN SYSTEMS

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(chemistry, coagulation, and morphology)

1040. Chieffi, M., and E. Kirk: Vitamin studies in middle-aged and old individuals. II. Correlation between vitamin A plasma content and certain clinical and laboratory findings. *J. Nutrit., 37:* 67-79, 1949. Abstr: *B. A., 23:* No. 28550, 1949.

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